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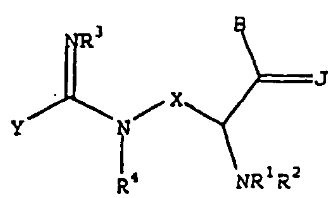

(I)

(57) Abstract

Amino acid heterocyclic amide derivatives useful as nitric oxide synthase inhibitors, having formula (I) and pharmaceutically acceptable salts and prodrugs, wherein: J is O or S; B is NR^5R^{11} wherein R^{11} is selected from a heterocyclic ring in which at least one member of the ring is carbon and in which 1 to about 4 heteroatoms are independently selected from oxygen, nitrogen and sulfur and said heterocyclic ring may be optionally substituted.

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NOVEL AMINO ACID HETEROCYCLIC AMIDE DERIVATIVES USEFUL AS NITRIC OXIDE SYNTHASE INHIBITORS

This application claims the benefit of priority to U.S. Provisional Application No. 60/106,514, filed October 30, 1998.

Background of the Invention

Field of the Invention

The present invention relates to novel amino acid heterocyclic amide derivatives and their use in therapy, in particular their use as nitric oxide synthase inhibitors.

Related Art

It has been known since the early 1980's that the vascular relaxation caused by acetylcholine is dependent on the presence of the vascular endothelium and this activity was ascribed to a labile humoral factor termed endothelium-derived relaxing factor (EDRF). The activity of nitric oxide (NO) as a vasodilator has been known for well over 100 years. In addition, NO is the active component of amylnitrite, glyceryltrinitrate and other nitrovasodilators. The recent identification of EDRF as NO has coincided with the discovery of a biochemical pathway by which NO is synthesized from the amino acid L-arginine by the enzyme NO synthase.

Nitric oxide is the endogenous stimulator of the soluble guanylate cyclase. In addition to endothelium-dependent relaxation, NO is involved in a number of biological actions including cytotoxicity of phagocytic cells and cell-to-cell communication in the central nervous system (see Moncada et al., Biochemical Pharmacology, 38, 1709-1715, 1989; Moncada et al., Pharmacological Reviews, 43, 109-142, 1991). Excess NO production appears to be involved in a number of pathological conditions, particularly conditions which involve systemic

hypotension such as toxic shock, septic shock and therapy with certain cytokines (Kerwin et al., J. Medicinal Chemistry, 38, 4343-4362, 1995).

The synthesis of NO from L-arginine can be inhibited by the L-arginine analogue, L-N-monomethyl-arginine (L-NMMA) and the therapeutic use of L-NMMA for the treatment of toxic shock and other types of systemic hypotension has been proposed (WO 91/04024 and GB-A-2240041). The therapeutic use of certain other NO synthase inhibitors apart from L-NMMA for the same purpose has also been proposed in WO 91/04024 and in EP-A-0446699.

It has recently become apparent that there are at least three types of NO synthase as follows:

(i) a constitutive, Ca++/calmodulin dependent enzyme, located in the endothelium, that releases NO in response to receptor or physical stimulation.

(ii) a constitutive, Ca++/calmodulin dependent enzyme, located in the brain, that releases NO in response to receptor or physical stimulation.

(iii) a Ca++ independent enzyme which is induced after activation of vascular smooth muscle,macrophages, endothelial cells, and a number of other cells by endotoxin and cytokines. Once expressed this inducible NO synthase generates NO continuously for long periods.

The NO released by the two constitutive enzymes acts as a transduction mechanism underlying several physiological responses. The NO produced by the inducible enzyme is a cytotoxic molecule for tumor cells and invading microorganisms. It also appears that the adverse effects of excess NO production, in particular pathological vasodilation and tissue damage, may result largely from the effects of NO synthesized by the inducible NO synthase (Knowles and Moncada, Biochem J., 298, 249-258, 1994 Billiar et al., Annals of Surgery, 221, 339-349, 1995; Davies et al., 1995)

There is also a growing body of evidence that NO may be involved in the degeneration of cartilage which takes place in cerain conditions such as arthritis and

it is also known that NO synthesis is increased in rheumatoid arthritis and in osteoarthritis (McInnes et al., J. Exp. Med, 184, 1519-1524, 1996; Sakurai et al., J. Clin. Investig., 96, 2357-2363, 1995). Accordingly, conditions in which there is an advantage in inhibiting NO production from L-arginine include autoimmune and/or inflammatory conditions affecting the joints, for example arthritis (especially osteoarthritis), and also inflammatory bowel disease, cardivascular ischemia, diabetes, congestive heart failure, myocarditis, atherosclerosis, migraine, glaucoma, reflux esophagitis, diarrhea, irritable bowel syndrome, cystic fibrosis, emphysema, asthma, bronchiectasis, hyperalgesia (allodynia), cerebral ischemia (both focal ischemia, thrombotic stroke and global ischemia (secondary to cardiac arrest), multiple sclerosis and other central nervous system disorders mediated by NO, for example Parkinson's disease and Alzheimer's disease, and other disorders mediated by NO including opiate tolerance in patients needing protracted opiate analgesics, and benzodiazepine tolerance in patients taking benzodiazepines, and other addictive behaviour, for example, nicotine and eating disorders (Kerwin et al., J. Medicinal Chemistry, 38, 4343-4362, 1995; Knowles and Moncada, Biochem J., 298, 249-258, 1994; Davies et al., 1995; Pfeilschifter et al., Cell Biology International, 20, 51-58, 1996).

Further conditions in which there is an advantage in inhibiting NO production from L-arginine include systemic hypotension associated with septic and/or toxic shock induced by a wide variety of agents; therapy with cytokines such as TNF, IL-1 and IL-2; and as an adjuvant to short term immunosuppression in transplant therapy (E. Kelly et al., J. Partent. Ent. Nutri., 19, 234-238, 1995; S. Moncada and E. Higgs, FASEB J., 9, 1319-1330, 1995; R. G. Kilbourn et al, Crit. Care Med., 23, 1018-1024, 1995).

Some of the NO synthase inhibitors proposed for therapeutic use so far, and in particular L-NMMA, are non-selective; they inhibit both the constitutive and the inducible NO synthases. Use of such a non-selective NO synthase inhibitor requires that great care be taken in order to avoid the potentially serious consequences of over-inhibition of the constitutive NO-synthase including hypertension and possible thrombosis and tissue damage. In particular, in the case

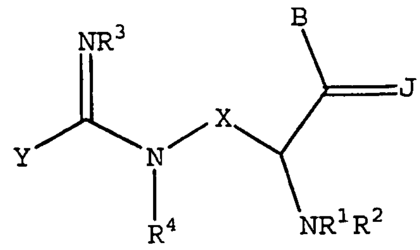
of the therapeutic use of L-NMMA for the treatment of toxic shock it has been recommended that the patient must be subject to continuous blood pressure monitoring throughout the treatment. Thus, while non-selective NO synthase inhibitors have therapeutic utility provided that appropriate precautions are taken, NO synthase inhibitors which are selective in the sense that they inhibit the inducible NO synthase to a considerably greater extent than the constitutive isoforms of NO synthase would be of even greater therapeutic benefit and easier to use (S. Moncada and E. Higgs, FASEB J., 9, 1319-1330, 1995).

WO 96/35677, WO 96/33175, WO 96/15120, WO 95/11014, WO 95/11231 WO 95/25717, WO 95/24382, WO94/12165, WO94/14780, WO93/13055, EP0446699A1 and U.S. Patent No. 5,132,453 disclose compounds that inhibit nitric oxide synthesis and preferentially inhibit the inducible isoform of nitric oxide synthase. The disclosures of which are hereby incorporated by reference in their entirety as if written herein.

Summary of the Invention

In a broad aspect, the present invention is directed to novel compounds, pharmaceutical compositions and methods of using said compounds and compositions for inhibiting or modulating nitric oxide synthesis in a subject in need of such inhibition or modulation by administering a compound which preferentially inhibits or modulates the inducible isoform of nitric oxide synthase over the constitutive isoforms of nitric oxide synthase. It is also another object of the present invention to lower nitric oxide levels in a subject in need of such lowering.

Compounds of the present invention are represented by the following chemical formula:



and pharmaceutically acceptable salts and prodrugs,

wherein:

J is O or S;

R^1 and R^2 are independently selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, hydroxyl, sulfhydryl, OR^6, SR^6, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, $CH_2SO_3^- M^+$, $CH_2CH_2SO_3^- M+$, $CH_2PO_3^{-2}\ 2M^+$, $CH_2CH_2PO_3^{-2}\ 2M^+$, $CH(OR^6)CF_3$, $S(O)R^{13}$, SO_2R^{13}, $P(O)(R^{30})_2$, $P(O)(R^{30})_3$, $C(O)R^{15}$, $C(S)R^{15}$, $CH_2OC(O)R^{15}$, $CH_2NR^{19}C(O)R^{15}$, $CH_2NR^{19}C(S)R^{15}$, $CH_2SC(O)R^{15}$, $CH_2SC(S)R^{15}$, $CH_2OC(O)GR^{15}$, $CH_2NR^{19}C(O)GR^{15}$, $CH_2NR^{19}C(S)GR^{15}$, $CH_2OC(S)GR^{15}$, $CH_2SC(S)GR^{15}$, OSO_2R^{13}, $OS(O)R^{13}$, $OC(S)R^{15}$, $SC(S)R^{15}$, $OC(S)GR^{15}$, $SC(S)GR^{15}$, $OC(O)R^{15}$, $SC(O)R^{15}$, $OC(O)GR^{15}$, $SC(O)GR^{15}$, and $R^{19}(R^{20})CH$; all, except hydrogen, alkyl, lower alkenyl, lower alkynyl, hydroxyl and sulfhydryl, may be optionally substituted by one or more alkyl, haloalkyl, aryl, hydroxyl, thiol, amino, alkylamino, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, carboxy, aryloxy,

heteroaryloxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups; provided that only one of R^1 and R^2 can be hydrogen, alkyl, alkenyl and alkynyl unless J is S; when J is O, R^3 and R^4 are independently selected to be other than hydrogen, lower alkyl, lower alkenyl, lower alkynyl, OR^6 wherein R^6 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl, SO_2R^{13} wherein R^{13} is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, and $C(O)R^{15}$, wherein R^{15} is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl, or B is NR^5R^{11} wherein R^5 is selected from other than the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl and aryl;

R^1 and R^2 can be taken together to form imines containing the substituent of formula $R^{19}(R^{20})C=$;

R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, hydroxyl, sulfhydryl, OR^6, SR^6, $CH_2SO_3^- M^+$, $CH_2CH_2SO_3^- M+$, $CH_2PO_3^{-2} 2M^+$, $CH_2CH_2PO_3^{-2} 2M^+$, $S(O)R^{13}$, SO_2R^{13}, $P(O)(R^{30})_2$, $P(O)(R^{30})_3$, $C(O)R^{15}$, $C(S)R^{15}$, $CH_2OC(O)R^{15}$, $CH_2NR^{19}C(O)R^{15}$, $CH_2NR^{19}C(S)R^{15}$, $CH_2SC(O)R^{15}$, $CH_2SC(S)R^{15}$, $CH_2OC(O)GR^{15}$, $CH_2NR^{19}C(O)GR^{15}$, $CH_2NR^{19}C(S)GR^{15}$, $CH_2OC(S)GR^{15}$, $CH_2SC(S)GR^{15}$, OSO_2R^{13}, $OS(O)R^{13}$, $OC(S)R^{15}$, $SC(S)R^{15}$, $OC(S)GR^{15}$, $SC(S)GR^{15}$, $OC(O)R^{15}$, $SC(O)R^{15}$, $OC(O)GR^{15}$, and $SC(O)GR^{15}$; provided that when J is O, R^6 cannot be lower alkyl, lower alkenyl, lower alkynyl or aryl and R^3 or R^4 cannot be OR^6; R^{13} cannot be lower alkyl, lower alkenyl, lower alkynyl or aryl when R^3

or R^4 is SO_2R^{13}, R^{15} cannot be lower alkyl, lower alkenyl, lower alkynyl or aryl when R^3 or R^4 is COR^{15}; provided only one of R^3 and R^4 can be hydrogen, lower alkyl, lower alkenyl, or lower alkynyl unless R^1 and R^2 are independently selected from other than hydrogen, alkyl, lower alkenyl, and lower alkynyl or B is NR^5R^{11} wherein R^5 is selected from other than the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl and aryl;

G is selected from the group consisting of O, S, CH_2, CHR^{15}, $C(R^{15})_2$, NH, and NR^{15};

R^6 is selected from the group consisting of hydroxyalkyl, heteroaryloxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and alkylpolyhydroxy;

R^{13} is selected from the group consisting of aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl,

alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxyusulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and alkylpolyhydroxy;

R^{15} is selected from the group consisting of hydrido, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino,

diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxyusulfonylalkylamino, aralkoxysulfonylalkýlamino, sulfonylalkylamino, natural and synthetic amino acids, and alkylpolyhydroxy;

M^+ is a pharmaceutically acceptable cation;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, and $-(CH_2)_pQ(CH_2)_r-$ wherein p is 1 to 3, r is 1 to 3 and Q is oxygen, C=O, and $S(O)_t$ wherein t is 0 to 2, groups which may be optionally substituted with one or more alkyl, alkoxy, hydroxy, sulfhydryl, halogen, trifluoromethyl, nitro, cyano, amino, $P(O)R^{21}$ wherein R^{21} is hydroxyl or alkyl which may be optionally substituted with one or more alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, amino, carboxy, or $N(R^{12})_n$ wherein n is 1 to 2 and R^{12} is hydrogen, oxy, hydroxyl or alkyl which may be optionally substituted with one or more alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, or amino; or

X is $-(CH_2)_sA(CH_2)_v-$ wherein s is O to 2, v is 0 to 2 and A is a 3 to 6 membered carbocyclic or heterocyclic ring, aromatic ring or heteroaromatic ring which may be optionally substituted with alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, and amino;

Y is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, cycloalkenyl, cycloalkenyloxy, alkenyloxyalkyl, alkylaminoalkyl, and NR^9R^{10} wherein R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, nitro, amino, hydroxy, alkoxy, aryl, heterocyclyl, and aralkyl; R^9 and R^{10} can be taken together to form spacer groups independently selected from a linear moiety having a chain length of

2 to 7 atoms to form a C3 to C8 saturated heterocyclyl or a C4 to C8 partially saturated heterocyclyl substituted independently and optionally with one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups;

B is NR^5R^{11} wherein R^5 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, hydroxyl, sulfhydryl, OR^6, SR^6, alkyl, alkenyl, alkynyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, $CH_2SO_3^- M^+$, $CH_2CH_2SO_3^- M+$, $CH_2PO_3^{-2}\ 2M^+$, $CH_2CH_2PO_3^{-2}\ 2M^+$, $CH(OR^6)CF_3$, $S(O)R^{13}$, SO_2R^{13}, $P(O)(R^{30})_2$, $P(O)(R^{30})_3$, $C(O)R^{15}$, $C(S)R^{15}$, $CH_2OC(O)R^{15}$, $CH_2NR^{19}C(O)R^{15}$, $CH_2NR^{19}C(S)R^{15}$, $CH_2SC(O)R^{15}$, $CH_2SC(S)R^{15}$, $CH_2OC(O)GR^{15}$, $CH_2NR^{19}C(O)GR^{15}$, $CH_2NR^{19}C(S)GR^{15}$, $CH_2OC(S)GR^{15}$, $CH_2SC(S)GR^{15}$, OSO_2R^{13}, $OS(O)R^{13}$, $OC(S)R^{15}$, $SC(S)R^{15}$, $OC(S)GR^{15}$, $SC(S)GR^{15}$, $OC(O)R^{15}$, $SC(O)R^{15}$, $OC(O)GR^{15}$, $SC(O)GR^{15}$, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboalkoxyalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl,

sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, optionally substituted with one or more alkyl, haloalkyl, aryl, hydroxyl, thiol, amino, alkylamino, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, carboxy, aryloxy, heteroaryloxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups, provided that R^5 is selected from other than the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl and aryl unless J is S; when J is O one of R^1 and R^2 is other than hydrogen, lower alkyl, lower alkenyl or lower alkynyl or one of R^3 and R^4 are independently selected to be other than hydrogen, lower alkyl, lower alkenyl, lower alkynyl, OR^6 wherein R^6 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl, SO_2R^{13} wherein R^{13} is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl, $C(O)R^{15}$, wherein R^{15} is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl;

R^5 and R^1 can be taken together to form a spacer group selected from a linear moiety having a chain length of 1 to 4 atoms to form a C5 to C8 saturated heterocyclyl or a C5 to C8 partially saturated heterocyclyl optionally substituted with one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups;

R^5 and R^2 can be taken together to form spacer group selected from a linear moiety having a chain length of 1 to 4 atoms to form a C5 to C8 saturated heterocyclyl or a C5 to C8 partially saturated heterocyclyl optionally substituted with one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups;

R^5 can be a spacer selected from a covalent bond or linear moiety having a chain length of 1 to 4 atoms to form a C5 to C10 saturated heterocyclyl or a C5 to C10 partially saturated heterocyclyl optionally substituted with one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups, and bonded to a hydroxyl, sulfhydryl, amino, carboxyl, or carbonyl substituent of group X,

R^{11} is selected from a heterocyclic ring in which at least one member of the ring is carbon and in which 1 to about 4 heteroatoms are independently selected from oxygen, nitrogen and sulfur and said heterocyclic ring may be optionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino,

diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, guanidino, amidino, and acylamino;

R^{19} and R^{20} are independently selected from the group consisting of hydrogen, hydroxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, acyl, aroyl, aralkanoyl, heteroaroyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, aralkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsufonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, dialkoxyphosphono, diaralkoxyphosphono, dialkoxyphosphonoalkyl, and diaralkoxyphosphonoalkyl provided that only one of R^{19} and R^{20} is hydrogen;

R^{19} and R^{20} can be taken together to form spacer groups independently selected from a linear moiety having a chain length of 2 to 7 atoms to form a C3 to C8 saturated cycloalkyl, a C3 to C8 partially saturated cycloalkyl, or a C3 to C8 heterocyclyl substituted independently and optionally with one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups;

R^{30} is selected from the group consisting of hydroxy, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxyusulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and polyhydroxy compounds of carbon.

It is an object of the present invention to provide compounds that have usefulness as inhibitors of nitric oxide synthase. These compounds also preferentially substantially inhibit the inducible form over the constitutive form.

It is an object of the present invention to provide compounds that also are more selective than those known in the art.

It is also an advantage that compounds of the present invention have preferred physical properties as compared to compounds known in the art. For example, NIL, which is disclosed in WO 93/13055 can be isolated as a colorless crystal, but has the property of deliquescence. The compound quickly becomes a

very viscous sticky oil upon exposure to moisture in normal room air which makes it difficult to handle.

Also included in the family of compounds of Formula 1, are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula 1 may be prepared from inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucoronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethylsulfonic, benzenesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula 1 include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethyleneldiamine, choline, chloroprocaine, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procain. All of these salts may be prepared by conventional means from the corresponding compound of Formula 1 by reacting, for example, the appropriate acid or base with the compound of Formula 1.

While it may be possible for the compounds of formula (1) to be administered as the raw chemical, it is preferable to present them as a pharmaceutical composition. According to a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (1) or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredient. The carrier(s) must be acceptable in the sense of being

compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of formula (1) or a pharmaceutically acceptable salt or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampuls and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavored basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbelow recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The compounds of the invention may be administered orally or via injection at a dose of from 0.001 to 2500 mg/kg per day. The dose range for humans is generally from 0.005 mg to 10 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.

The compounds of formula (1) are preferably administered orally or by injection (intravenous or subcutaneous). The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity. Also, the route of administration may vary depending on the condition and its severity.

As utilized herein, the term “lower alkyl”, alone or in combination, means an acyclic unsubstituted alkyl radical containing from 1 to about 10, preferably from 1 to about 8 carbon atoms and more preferably 1 to about 6 carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like.

As utilized herein, the term “alkyl”, alone or in combination, means an acyclic alkyl radical containing from 1 to about 10, preferably from 1 to about 8 carbon atoms and more preferably 1 to about 6 carbon atoms. Said alkyl radicals may be optionally substituted with groups as defined below. Examples of such radicals include methyl, ethyl, chloroethyl, hydroxyethyl, n-propyl, oxopropyl, isopropyl, n-butyl, cyanobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, aminopentyl, iso-amyl, hexyl, octyl and the like.

The term "lower alkenyl" refers to an unsaturated, unsubstituted acyclic hydrocarbon radical in so much as it contains at least one double bond. Such radicals containing from about 2 to about 10 carbon atoms, preferably from about 2 to about 8 carbon atoms and more preferably 2 to about 6 carbon atoms. Examples of suitable alkenyl radicals include propylenyl, buten-1-yl, isobutenyl, pentenylen-l-yl, 2-2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, hepten-1-yl, and octen-1-yl, and the like.

The term "alkenyl" refers to an unsaturated, acyclic hydrocarbon radical in so much as it contains at least one double bond. Such radicals containing from about 2 to about 10 carbon atoms, preferably from about 2 to about 8 carbon atoms and more preferably 2 to about 6 carbon atoms. Said alkenyl radicals may be

optionally substituted with groups as defined below. Examples of suitable alkenyl radicals include propylenyl, 2-chloropropylenyl, buten-1-yl, isobutenyl, pentenylen-1-yl, 2-2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-hydroxyhexen-1-yl, hepten-1-yl, and octen-1-yl, and the like.

The term "lower alkynyl" refers to an unsaturated, unsubstituted acyclic hydrocarbon radical in so much as it contains one or more triple bonds, such radicals containing about 2 to about 10 carbon atoms, preferably having from about 2 to about 8 carbon atoms and more preferably having 2 to about 6 carbon atoms. Examples of suitable alkynyl radicals include ethynyl, propynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals and the like.

The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical in so much as it contains one or more triple bonds, such radicals containing about 2 to about 10 carbon atoms, preferably having from about 2 to about 8 carbon atoms and more preferably having 2 to about 6 carbon atoms. Said alkynyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals and the like.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a "hydroxyl" radical, one hydrido radical may be attached to a carbon atom to form a "methine" radical $(-\overset{|}{C}H-)$, or two hydrido radicals may be attached to a carbon atom to form a "methylene" ($-CH_2-$) radical.

The term "carbon" radical denotes a carbon atom without any covalent bonds and capable of forming four covalent bonds.

The term “cyano” radical denotes a carbon radical having three of four covalent bonds shared by a nitrogen atom.

The term "hydroxyalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with a hydroxyl as defined above. Specifically embraced are monohydroxyalkyl, dihydroxyalkyl and polyhydroxyalkyl radicals.

The term "alkanoyl" embraces radicals wherein one or more of the terminal alkyl carbon atoms are substituted with one or more carbonyl radicals as defined below. Specifically embraced are monocarbonylalkyl and dicarbonylalkyl radicals. Examples of monocarbonylalkyl radicals include formyl, acetyl, and pentanoyl. Examples of dicarbonylalkyl radicals include oxalyl, malonyl, and succinyl.

The term “alkylene” radical denotes linear or branched radicals having from 1 to about 10 carbon atoms and having attachment points for two or more covalent bonds. Examples of such radicals are methylene, ethylene, methylethylene, and isopropylidene.

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred haloalkyl radicals are "lower haloalkyl" radicals having one to about six carbon atoms. Examples of such haloalkyl

radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

The term "hydroxyhaloalkyl" embraces radicals wherein any one or more of the haloalkyl carbon atoms is substituted with hydroxy as defined above.

The term “haloalkylene radical” denotes alkylene radicals wherein any one or more of the alkylene carbon atoms is substituted with halo as defined above. Dihalo alkylene radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkylene radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred haloalkylene radicals are "lower haloalkylene" radicals having one to about six carbon atoms. Examples of “haloalkylene” radicals include difluoromethylene, tetrafluoroethylene, tetrachloroethylene, alkyl substituted monofluoromethylene, and aryl substituted trifluoromethylene.

The term “haloalkenyl” denotes linear or branched radicals having from 1 to about 10 carbon atoms and having one or more double bonds wherein any one or more of the alkenyl carbon atoms is substituted with halo as defined above. Dihaloalkenyl radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkenyl radicals may have more than two of the same halo atoms or a combination of different halo radicals.

The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. More preferred alkoxy radicals

are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy alkyls. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, difluoromethoxy, trifluoroethoxy, fluoroethoxy, tetrafluoroethoxy, pentafluoroethoxy, and fluoropropoxy.

The term "haloalkoxyalkyl" also embraces alkyl radicals having one or more haloalkoxy radicals attached to the alkyl radical, that is, to form monohaloalkoxyalkyl and dihaloalkoxyalkyl radicals. The term "haloalkenyloxy" also embraces oxygen radicals having one or more haloalkenyloxy radicals attached to the oxygen radical, that is, to form monohaloalkenyloxy and dihaloalkenyloxy radicals.

The term "haloalkenyloxyalkyl" also embraces alkyl radicals having one or more haloalkenyloxy radicals attached to the alkyl radical, that is, to form monohaloalkenyloxyalkyl and dihaloalkenyloxyalkyl radicals.

The term “alkylenedioxy” radicals denotes alkylene radicals having at least two oxygens bonded to a single alkylene group. Examples of “alkylenedioxy” radicals include methylenedioxy, ethylenedioxy, alkylsubstituted methylenedioxy, and arylsubstituted methylenedioxy. The term “haloalkylenedioxy” radicals denotes haloalkylene radicals having at least two oxy groups bonded to a single haloalkyl group. Examples of “haloalkylenedioxy” radicals include difluoromethylenedioxy, tetrafluoroethylenedioxy, tetrachluoroethylenedioxy, alkylsubstituted monofluoromethylenedioxy, and arylsubstituted monofluoromethylenedioxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces

aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Said "aryl" group may have 1 to 3 substituents such as heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy. The term "perhaloaryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl wherein the aryl radical is substituted with 3 or more halo radicals as defined above.

The term "heterocyclyl" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms[e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocyclyl radicals include dihydrothiophene,

dihydropyran, dihydrofuran and dihydrothiazole. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclyl" group may have 1 to 3 substituents as defined below. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. Non-limiting examples of heterocyclic radicals include pyrrolyl, pyridinyl, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrazolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolindinyl, 1,3-dioxolanyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-

triazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazonyl, quinolinyl, tetraazolyl, and the like.

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. "alkylsulfonylalkyl", embraces alkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above. "haloalkylsulfonyl", embraces haloalkyl radicals attached to a sulfonyl radical, where haloalkyl is defined as above. "haloalkylsulfonylalkyl", embraces haloalkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above. The term “aminosulfonyl” denotes an amino radical attached to a sulfonyl radical.

The term "sulfinyl", whether used alone or linked to other terms such as alkylsulfinyl, denotes respectively divalent radicals -S(O)-. "alkylsulfinyl", embraces alkyl radicals attached to a sulfinyl radical, where alkyl is defined as above. "alkylsulfinylalkyl", embraces alkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above. "haloalkylsulfinyl", embraces haloalkyl radicals attached to a sulfinyl radical, where haloalkyl is defined as above. "haloalkylsulfinylalkyl", embraces haloalkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl and diphenylethyl. The aryl in said aralkyl may have additional substituents such as heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio,

alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy. The terms benzyl and phenylmethyl are interchangeable.

The term "heteroaralkyl" embraces heteroaryl-substituted alkyl radicals wherein the heteroaralkyl radical may be additionally substituted with three or more substituents as defined above for aralkyl radicals. The term "perhaloaralkyl" embraces aryl-substituted alkyl radicals wherein the aralkyl radical is substituted with three or more halo radicals as defined above.

The term "aralkylsulfinyl" embraces aralkyl radicals attached to a sulfinyl radical, where aralkyl is defined as above. "aralkylsulfinylalkyl", embraces aralkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "aralkylsulfonyl", embraces aralkyl radicals attached to a sulfonyl radical, where aralkyl is defined as above. "Aralkylsulfonylalkyl", embraces aralkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "cycloalkyl" embraces radicals having three to ten carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals. Preferable cycloalkylalkyl radicals are "lower cycloalkylalkyl" radicals having cycloalkyl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include cyclohexylhexyl. The term "cycloalkenyl" embraces radicals having three to ten carbon atoms and one or more carbon-carbon double bonds. Preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl. The term "halocycloalkyl" embraces radicals wherein any one or more of the cycloalkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohalocycloalkyl, dihalocycloalkyl and polyhalocycloalkyl radicals. A monohalocycloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhalocycloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred halocycloalkyl radicals are "lower halocycloalkyl" radicals having three to about eight carbon atoms. Examples of such halocycloalkyl radicals include fluorocyclopropyl, difluorocyclobutyl, trifluorocyclopentyl, tetrafluorocyclohexyl, and dichlorocyclopropyl. The term "halocycloalkenyl" embraces radicals wherein any one or more of the cycloalkenyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohalocycloalkenyl, dihalocycloalkenyl and polyhalocycloalkenyl radicals. The term "halocycloalkoxy" also embraces cycloalkoxy radicals having one or more halo radicals attached to the cycloalkoxy radical, that is, to form monohalocycloalkoxy, dihalocycloalkoxy, and polycycloalkoxy radicals.

The term "cycloalkylsulfinyl", embraces cycloalkyl radicals attached to a sulfinyl radical, where cycloalkyl is defined as above. "cycloalkylsulfinylalkyl", embraces cycloalkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above. The term "cycloalkylsulfonyl", embraces cycloalkyl radicals attached to a sulfonyl radical, where cycloalkyl is defined as above. "cycloalkylsulfonylalkyl", embraces cycloalkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having one to six carbon atoms. An example of "lower alkylthio" is methylthio (CH_3-S-). The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- atom.

The terms alkylamino denotes "monoalkylamino" and "dialkylamino" containing one or two alkyl radicals, respectively, attached to an amino radical. The terms arylamino denotes "monoarylamino" and "diarylamino" containing one or two aryl radicals, respectively, attached to an amino radical. The term "Aralkylamino", embraces aralkyl radicals attached to an amino radical, where aralkyl is defined as above. The term aralkylamino denotes "monoaralkylamino" and "diaralkylamino" containing one or two aralkyl radicals, respectively, attached to an amino radical. The term aralkylamino further denotes "monoaralkyl monoalkylamino" containing one aralkyl radical and one alkyl radical attached to an amino radical.

The term "arylsulfinyl" embraces radicals containing an aryl radical, as defined above, attached to a divalent -S(=O)- atom. The term "arylsulfinylalkyl" denotes arylsulfinyl radicals attached to a linear or branched alkyl radical, of one to ten carbon atoms.

The term "arylsulfonyl", embraces aryl radicals attached to a sulfonyl radical, where aryl is defined as above. "arylsulfonylalkyl", embraces arylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above. The term "heteroarylsulfinyl" embraces radicals containing an heteroaryl radical, as defined above, attached to a divalent -S(=O)- atom. The term "heteroarylsulfinylalkyl" denotes heteroarylsulfinyl radicals attached to a linear or branched alkyl radical, of one to ten carbon atoms. The term "heteroarylsulfonyl", embraces heteroaryl radicals attached to a sulfonyl radical, where heteroaryl is defined as above. "heteroarylsulfonylalkyl", embraces heteroarylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "aryloxy" embraces aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy. The aryl in said aryloxy may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "aroyl" embraces aryl radicals, as defined above, attached to an carbonyl radical as defined above. Examples of such radicals include benzoyl and toluoyl. The aroyl in said aroyl may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "aralkanoyl" embraces aralkyl radicals, as defined herein, attached to an carbonyl radical as defined above. Examples of such radicals include, for example, phenylacetyl. The aryl in said aralalkanoyl may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl,

aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having phenyl radicals attached to lower alkoxy radical as described above. The aryl in said aralkoxy radicals may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "aryloxyalkyl" embraces aryloxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenoxymethyl. The aryl in said aryloxyalkyl may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "haloaryloxyalkyl" embraces aryloxyalkyl radicals, as defined above, wherein one to five halo radicals are attached to an aryloxy group. The term "heteroaryloxy" embraces heteroaryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include pyridyloxy and furyloxy. The heteroaryl in said heteroaryloxy may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl,

arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "heteroaroyl" embraces heteroaryl radicals, as defined above, attached to an carbonyl radical as defined above. Examples of such radicals include furoyl and nicotinyl. The heteroaryl in said heteroaroyl may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "heteroaralkanoyl" embraces heteroaralkyl radicals, as defined herein, attached to an carbonyl radical as defined above. Examples of such radicals include, for example, pyridylacetyl and furylbutyryl. The heteroaryl in said heteroaralalkanoyl may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "heteroaralkoxy" embraces oxy-containing heteroaralkyl radicals attached through an oxygen atom to other radicals. More preferred heteroaralkoxy radicals are "lower heteroaralkoxy" radicals having heteroaryl radicals attached to lower alkoxy radical as described above. The heteroaryl in said heteroaralkoxy radicals may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl,

arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy. The term "heteroaryloxyalkyl" embraces heteroaryloxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include pyridyloxymethyl. The heteroaryl in said heteroaryloxyalkyl may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy. The term "haloheteroaryloxyalkyl" embraces heteroaryloxyalkyl radicals, as defined above, wherein one to four halo radicals are attached to an heteroaryloxy group.

The term "arylthio" embraces aryl radicals, as defined above, attached to an sulfur atom. Examples of such radicals include phenylthio. The aryl in said arylthio may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "arylthioalkyl" embraces arylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenylthiomethyl. The aryl in said arylthioalkyl may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl,

alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "alkylthioalkyl" embraces alkylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include methylthiomethyl. The term "alkoxyalkyl" embraces alkoxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include methoxymethyl.

The term “carbonyl” denotes a carbon radical having two of the four covalent bonds shared with an oxygen atom. The term “carboxy” embraces a hydroxyl radical, as defined above, attached to one of two unshared bonds in a carbonyl group. The term “carboxamide” embraces amino, monoalkylamino, and dialkylamino radicals, attached to one of two unshared bonds in a carbonyl group. The term “carboxamidoalkyl” embraces carboxamide radicals, as defined above, attached to an alkyl group. The term “carboxyalkyl” embraces a carboxy radical, as defined above, attached to an alkyl group. The term “carboalkoxy” embraces alkoxy radicals, as defined above, attached to one of two unshared bonds in a carbonyl group. The term “carboaralkoxy” embraces aralkoxy radicals, as defined above, attached to one of two unshared bonds in a carbonyl group. The term “monocarboalkoxyalkyl” embraces one carboalkoxy radical, as defined above, attached to an alkyl group. The term “dicarboalkoxyalkyl” embraces two carboalkoxy radicals, as defined above, attached to an alkylene group. The term “monocyanoalkyl” embraces one cyano radical, as defined above, attached to an alkyl group. The term “dicyanoalkylene” embraces two cyano radicals, as defined above, attached to

an alkyl group. The term "carboalkoxycyanoalkyl" embraces one cyano radical, as defined above, attached to an alkylene group.

The term "acyl", alone or in combination, means a carbonyl or thionocarbonyl group bonded to a radical selected from, for example, hydrido, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, alkoxyalkyl, haloalkoxy, aryl, heterocyclyl, heteroaryl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, alkylthio, arylthio, amino, alkylamino, dialkylamino, aralkoxy, arylthio, and alkylthioalkyl. Examples of "acyl" are formyl, acetyl, benzoyl, trifluoroacetyl, phthaloyl, malonyl, nicotinyl, and the like. The term "haloalkanoyl" embraces one or more halo radicals, as defined herein, attached to an alkanoyl radical as defined above. Examples of such radicals include, for example, chloroacetyl, trifluoroacetyl, bromopropanoyl, and heptafluorobutyryl. The alkanoyl in said haloalkanoyl may be additionally substituted with hydroxy, amino, thio, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "phosphono" embraces a pentavalent phosphorus attached with two covalent bonds to an oxygen radical. The term "dialkoxyphosphono" denotes

two alkoxy radicals, as defined above, attached to a phosphono radical with two covalent bonds. The term "diaralkoxyphosphono" denotes two aralkoxy radicals, as defined above, attached to a phosphono radical with two covalent bonds. The term "dialkoxyphosphonoalkyl" denotes dialkoxyphosphono radicals, as defined above, attached to an alkyl radical. The term "diaralkoxyphosphonoalkyl" denotes diaralkoxyphosphono radicals, as defined above, attached to an alkyl radical.

The structural term, H(W)C=C(K)E, alone or in combination, means a precursor to cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, cyanocarboalkoxycycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, or acylalkyl wherein at least one of W, E, and K are independently selected from carboxy, thionocarboxy, thiolcarboxy, cyano, carboxamido, thionocarboxamido, carboalkoxy, thionocarboalkoxy, thiocarboalkoxy, acyl, thionoacyl, formyl or thionoformyl provided any two of W, E, and K may be taken together to form a spacer group selected from a linear moiety having a chain length of 1 to 4 atoms to form a C5 to C8 saturated cycloalkyl, a C5 to C8 cycloalkyl, and a C5 to C8 heterocyclyl substituted independently and optionally with, for example, one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups;

Suitable substituents for the groups of the compounds of the present invention include, for example, heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl,

heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, carbohaloalkoxy, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, guanidino, amidino, and acylamino.

The term "spacer" can include a covalent bond and a linear moiety having a backbone of 1 to 7 continuous atoms. The spacer may have 1 to 7 atoms of a monovalent or multi-valent chain. Univalent chains may be constituted by a radical selected from =C(H)-, =C(R^6)-, -O-, -S-, -S(O)-, -S$(O)_2$-, -NH-, -N(R^6)-,-N=, -CH(OH)-, =C(OH)-, -CH(OR^6)-, =C(OR^6)-, and -C(O)-. Multi-valent chains may consist of a straight chain of 1, 2, 3, 4, 5, 6 or 7 atoms or a straight chain of 1, 2, 3, 4, 5, 6 or 7 atoms with a side chain. The chain may be constituted of one or more radicals selected from: lower alkylene, lower alkenyl, -O-, -O-CH_2-, -S-CH_2-, -CH_2CH_2-, ethenyl, -CH=CH(OH)-, -OCH_2O-, -O$(CH_2)_2$O-, -$NHCH_2$-, -OCH(R^6)O-, -O(CH_2CHR^6)O-, -OCF_2O-, -O$(CF_2)_2$O-, -S-, -S(O)-, -S$(O)_2$-, -N(H)-, -N(H)O-, -N(R^6)O-, -N(R^6)-, -C(O)-, -C(O)NH-, -C(O)NR^6-, -N=, -OCH_2-, -SCH_2-, S(O)CH_2-, -CH_2C(O)-, -CH(OH)-, =C(OH)-, -CH(OR^6)-, =C(OR^6)-, S$(O)_2CH_2$-, and -NR^6CH_2- and many others radicals defined above or generally known or ascertained by one of skill-in-the art. Side chains may include substituents

such as heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "prodrug" refers to a compound that is made more active in vivo.

As used herein, reference to "treatment" of a patient is intended to include prophylaxis.

All references, patents or applications, U.S. or foreign, cited in the application are hereby incorporated by reference as if written herein.

Compounds of the present invention can exist in tautomeric, geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-geometric isomers, E- and Z-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof and other mixtures thereof, as falling within the scope of the invention. Pharmaceutically acceptable sales of such tautomeric, geometric or stereoisomeric are also included within the invention.

The terms "cis" and "trans" denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have two high ranking groups on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans"). Some of the compounds described contain alkenyl groups, and are meant to include both cis and trans or "E" and "Z" geometric forms.

Some of the compounds described contain one or more stereocenters and are meant to include R, S, and mixtures of R and S forms for each stereocenter present.

Some of the compounds described herein may contain one or more ketonic or aldehydic carbonyl groups or combinations thereof alone or as part of a heterocyclic ring system. Such carbonyl groups may exist in part or principally in the "keto" form and in part or principally as one or more "enol" forms of each aldehyde and ketone group present. Compounds of the present invention having aldehydic or ketonic carbonyl groups are meant to include both "keto" and "enol" tautomeric forms.

Some of the compounds described herein may contain one or more imine or enamine groups or combinations thereof. Such groups may exist in part or principally in the "imine" form and in part or principally as one or more "enamine" forms of each group present. Compounds of the present invention having said imine or enamine groups are meant to include both "imine" and "enamine" tautomeric forms.

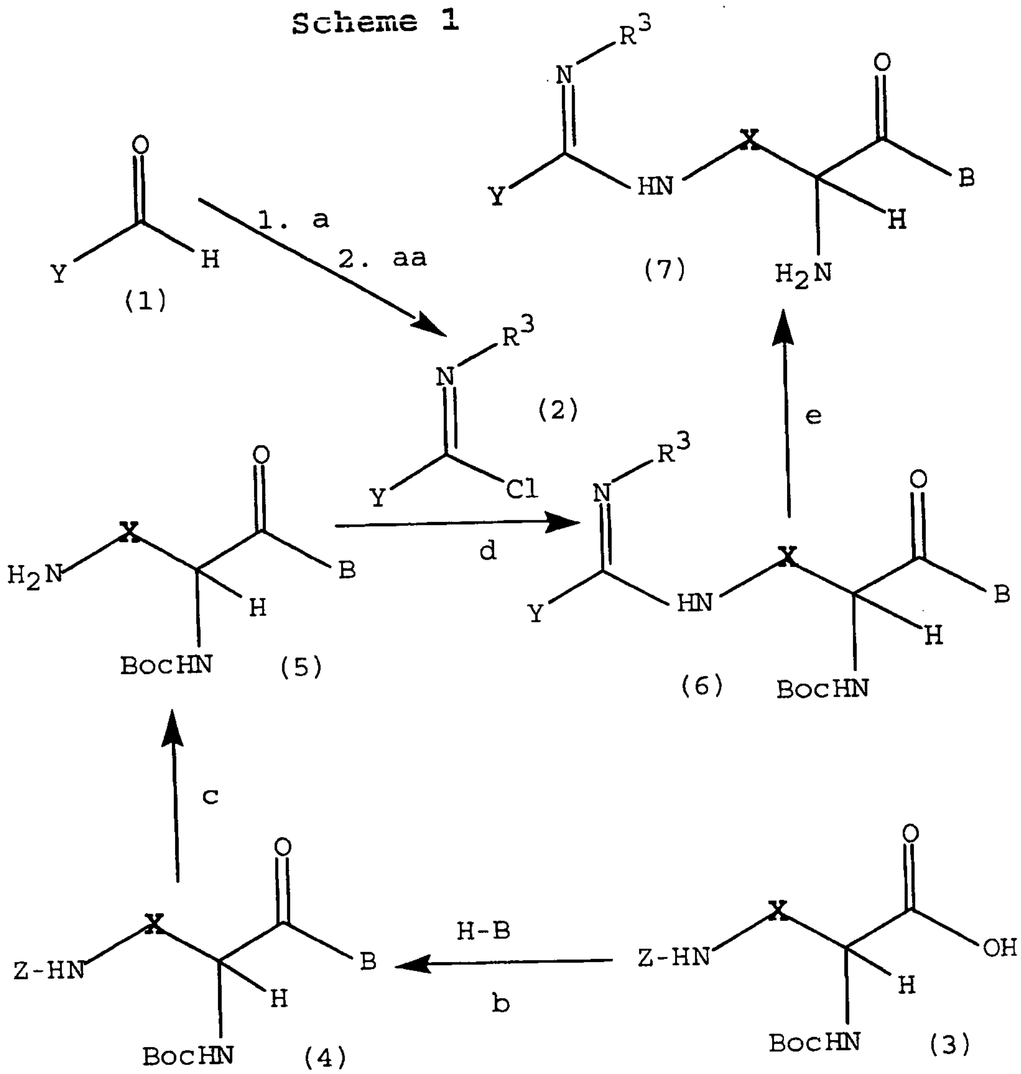
The following general synthetic sequences are useful in making the present invention. Abbreviations used in the schemes are as follows: "AA" represents amino acids, "Boc" represents tert-butyloxycarbonyl, "BOP" represents benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphonium hexafluorophosphate, "CMR-Cl" represents a chloromethylation or bromomethylation reagent such as Cl-$CH_2OC(O)R^{15}$, Cl-$CH_2NR^{19}C(O)R^{15}$, Cl-$CH_2NR^{19}C(S)R^{15}$, Cl-$CH_2SC(O)R^{15}$, Cl-$CH_2SC(S)R^{15}$, Cl-$CH_2OC(O)GR^{15}$, Cl-

$CH_2NR^{19}C(O)GR^{15}$, Cl-$CH_2NR^{19}C(S)GR^{15}$, Cl-$CH_2OC(S)GR^{15}$, or Cl-$CH_2SC(S)GR^{15}$, "DIPEA" represents diisopropylethylamine, "DMF" represents dimethylformamide, "Fmoc" represents 9-fluorenylmethoxycarbonyl, "LDA" represents lithium diisopropylamide, "PHTH" represents a phthaloyl group, "pnZ" represents 4-nitrobenzyloxycarbonyl, "p-TsOH" represents paratoluenesulfonic acid, "TBTU" represents 2-(1H-benzotriozole-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate, "TEA" represents triethylamine, "THF" represents tetrahydrofuran, and "Z" represents benzyloxycarbonyl.

Disclosed are thirty synthetic processes useful in the preparation of the compounds of the present invention. The use of "E" in the structures of these preparatory methods refers to the substituent "E" as defined in structural term, H(W)C=C(K)E, above. The use of "Z" in the structures of these preparatory methods refers to the use of the benzyloxycarbonyl group as defined in the paragraph immediately above.

The following examples are provided to illustrate the present invention and are not intended to limit the scope thereof. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

Scheme 1



(a) R^3-NH_2 (aa) N-chlorosuccimide, DMF

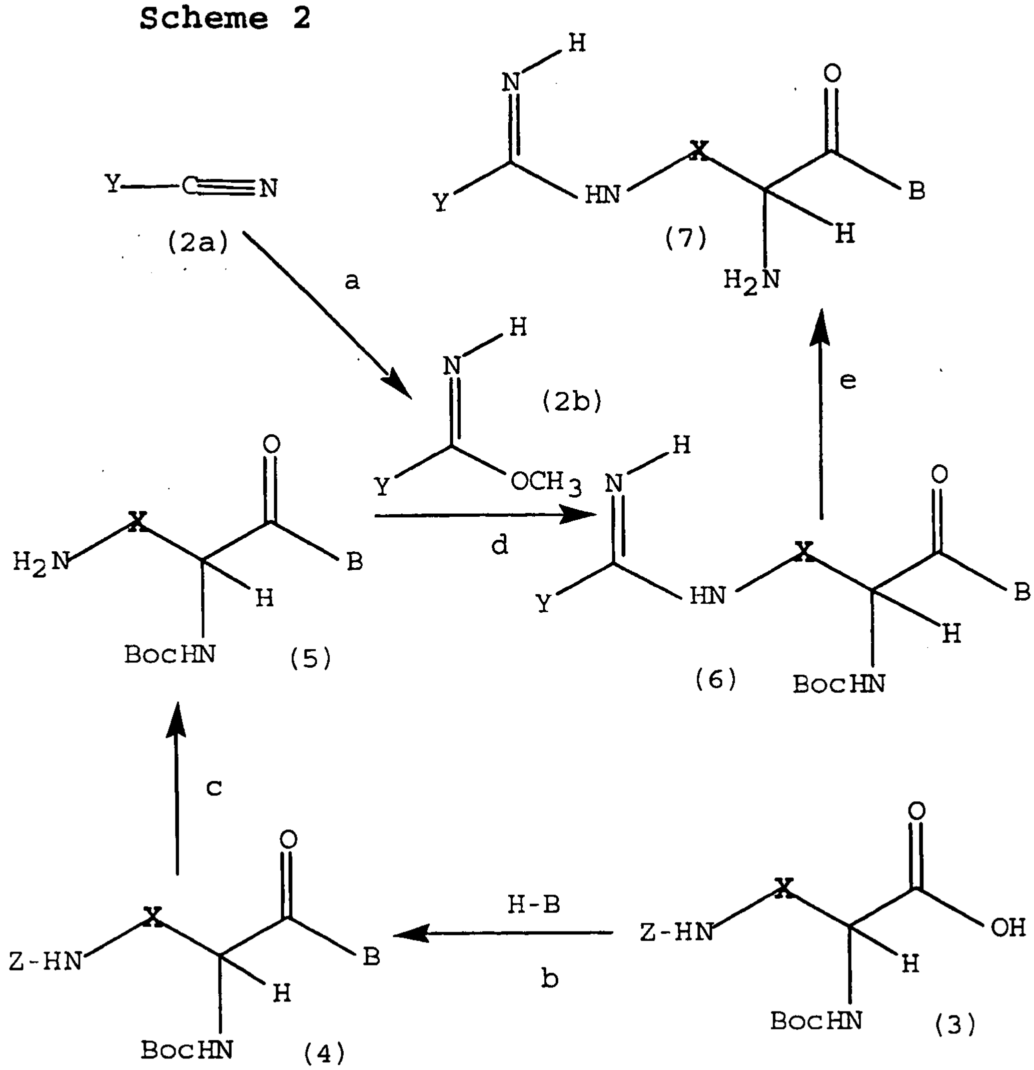
(b) BOP, DIPEA, DMF

(c) Pd, H_2, Ethanol/Acetic Acid

(d) H_2O, pH 9-10

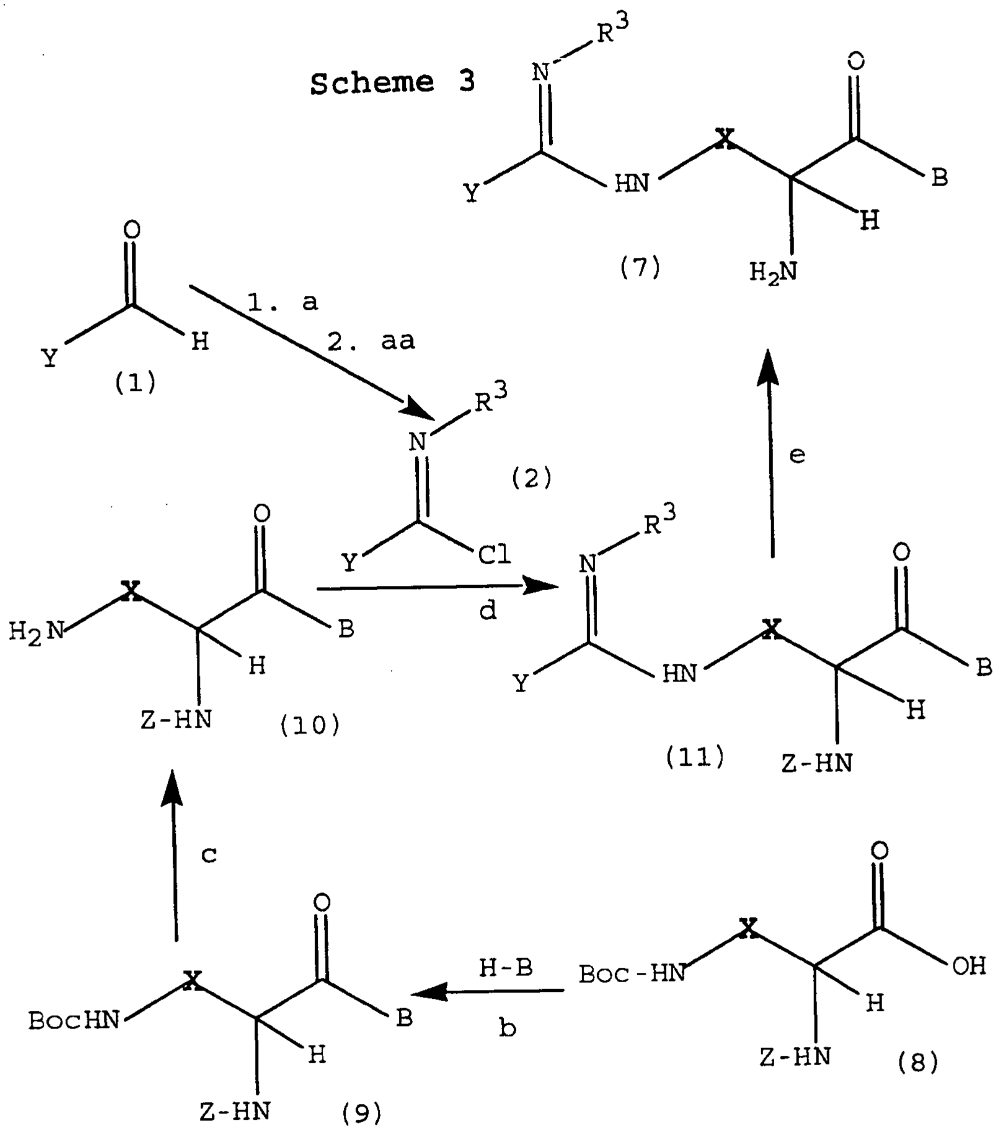
(e) HCl, dioxane or trifluoroacetic acid.

Scheme 2



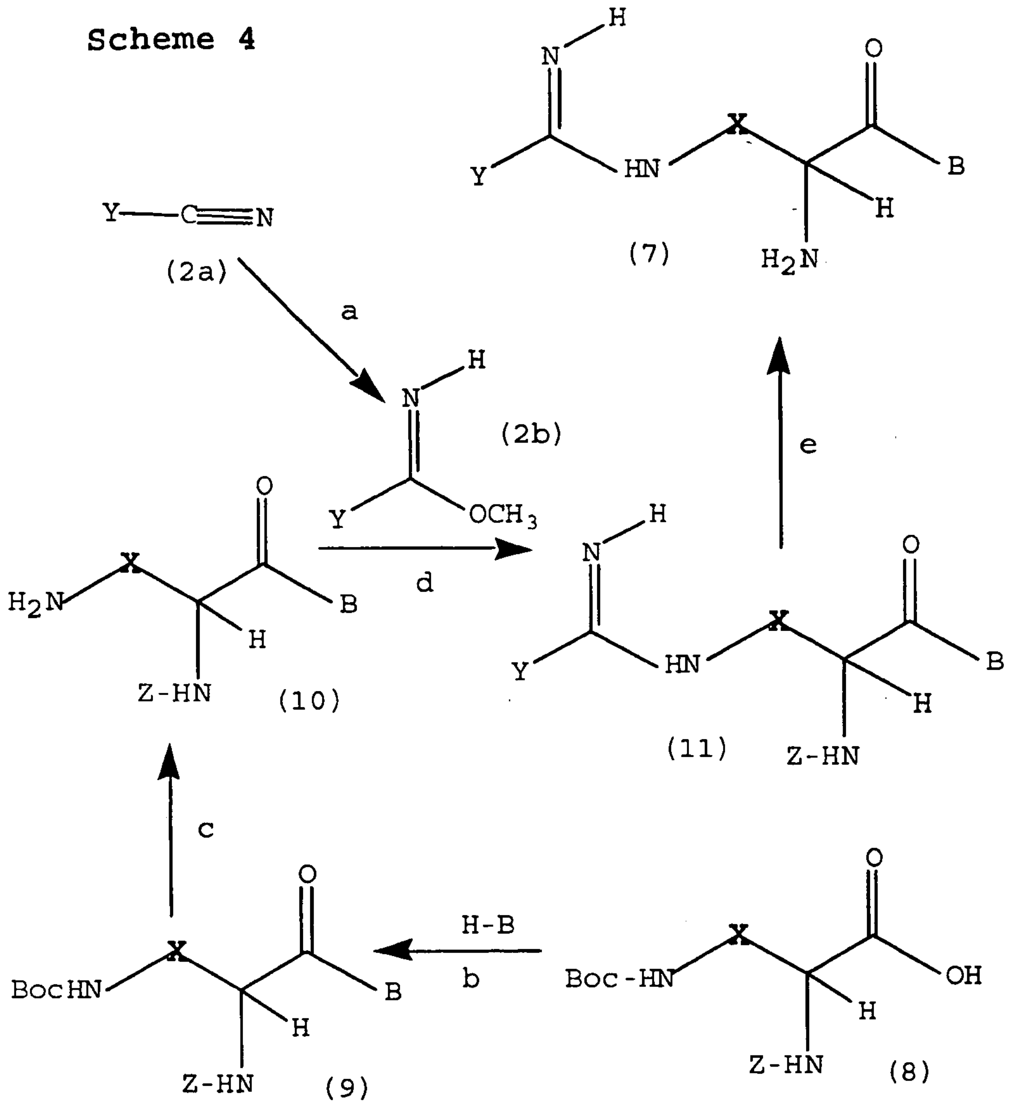
(a) HCl, Methanol
(b) BOP, DIPEA, DMF
(c) Pd, H_2, Ethanol/Acetic Acid
(d) TEA, DMF
(e) HCl, dioxane or trifluoroacetic acid.

Scheme 3



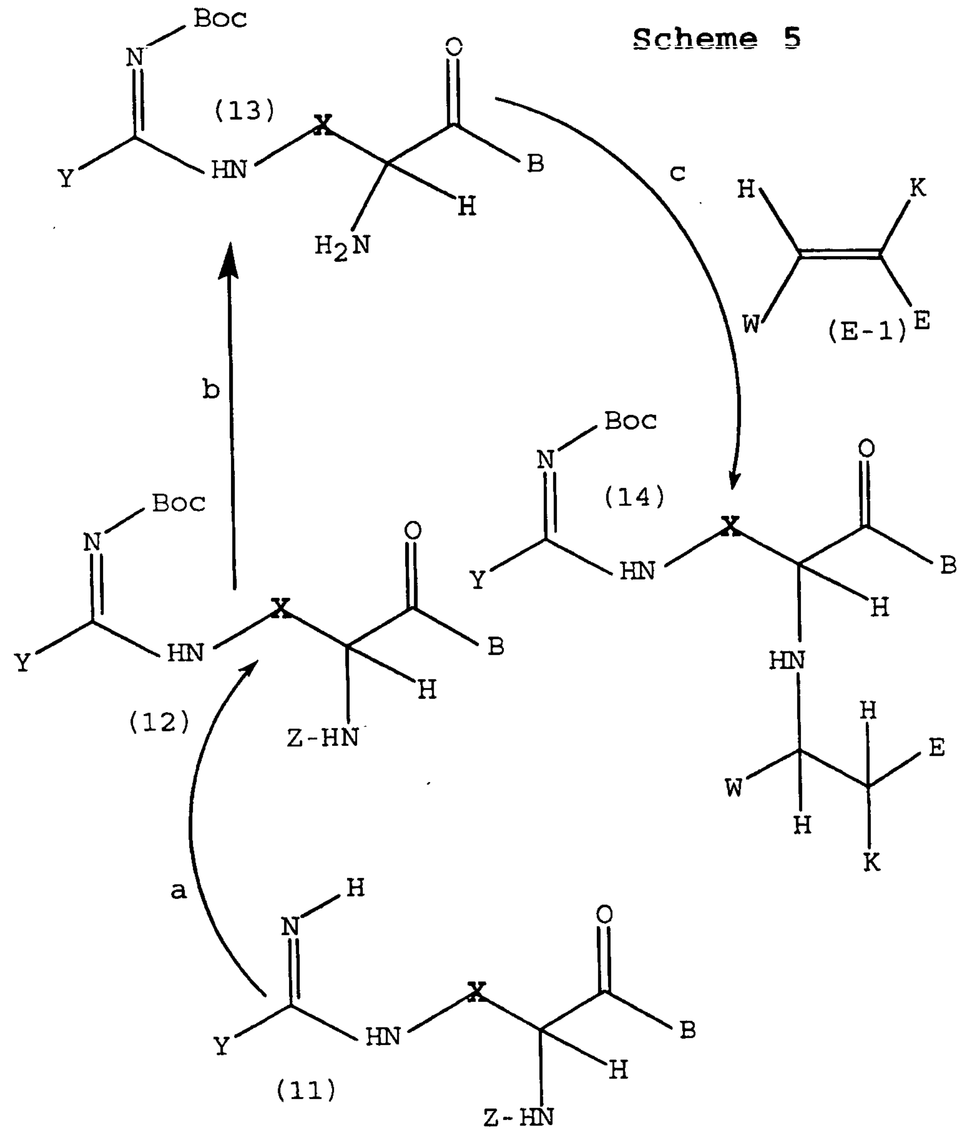
(a) R_3-NH_2 (aa) N-chlorosuccimide, DMF
(b) BOP, DIPEA, DMF
(c) HCl, dioxane or trifluoroacetic acid
(d) H_2O, pH 9-10 (e) Pd, H_2, Ethanol/Acetic Acid.

Scheme 4



(a) HCl, Methanol
(b) BOP, DIPEA, DMF
(c) HCl, dioxane or trifluoroacetic acid
(d) TEA, DMF
(e) Pd, H_2, Ethanol/Acetic Acid

Scheme 5

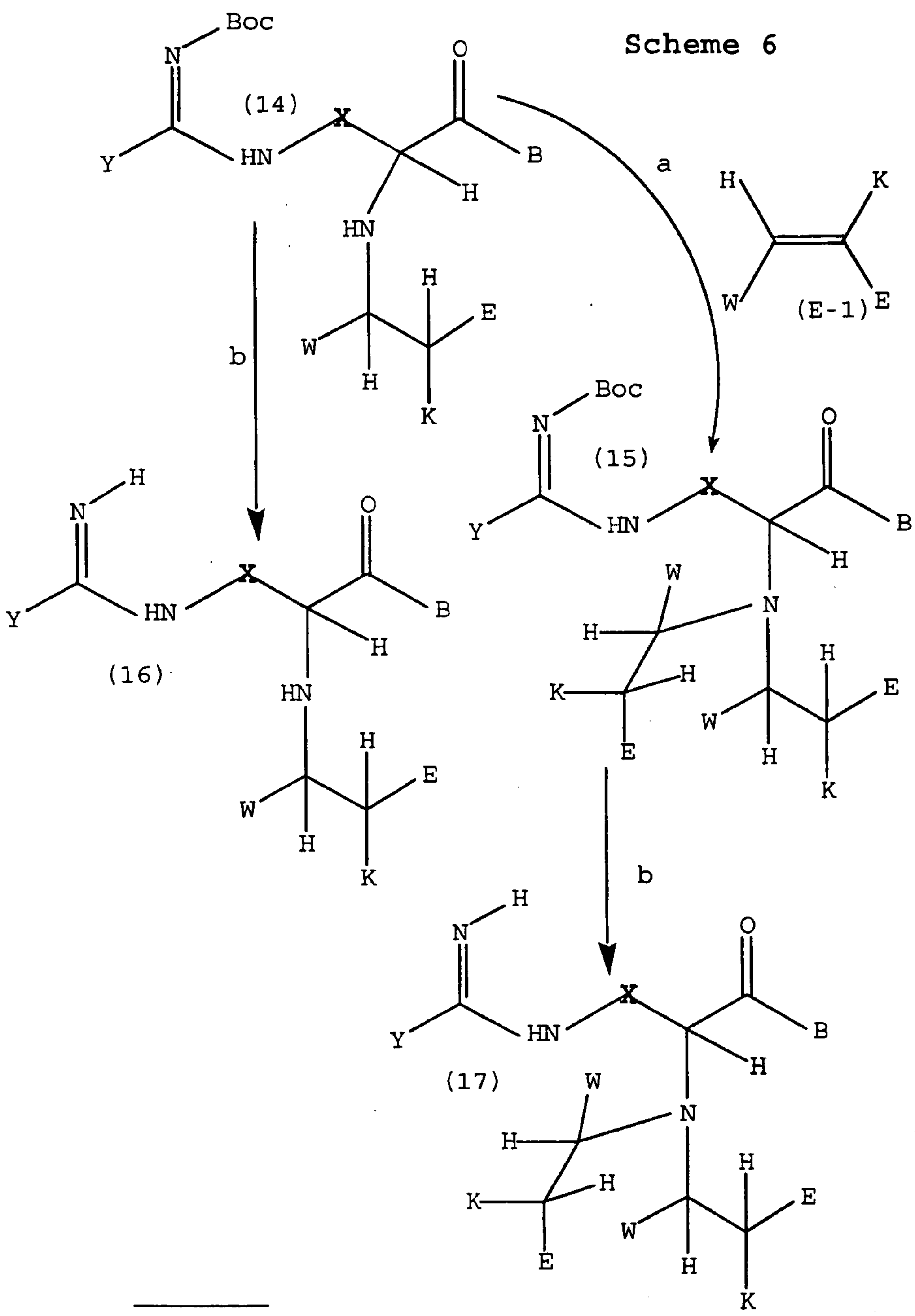


(a) t-Butoxycarbonyl azide, H_2O, dioxane, MgO

(b) Pd, H_2, Ethanol/Acetic Acid

(c) TEA, 0-80 °C

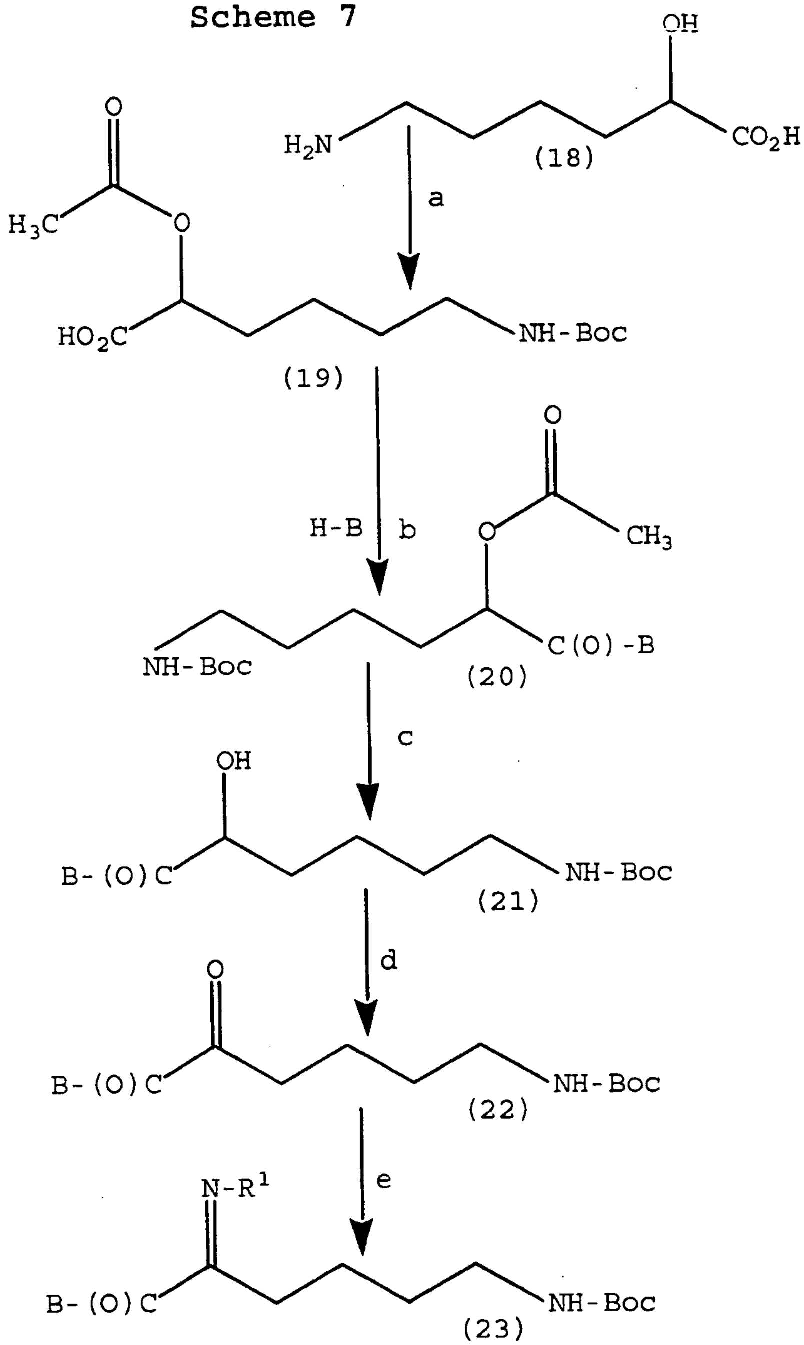
Scheme 6



(a) TEA, 0-80 °C

(b) HCl, dioxane

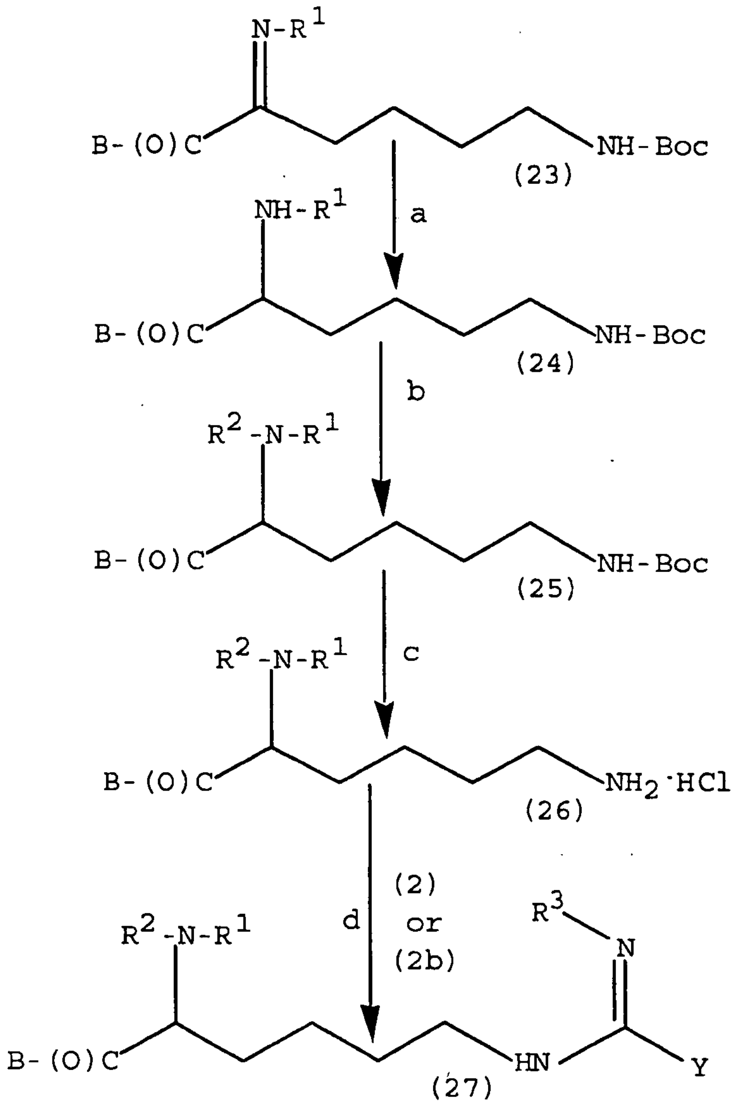
Scheme 7



(R^1= hydroxyl, sulfhydryl, OR^6 or SR^6)

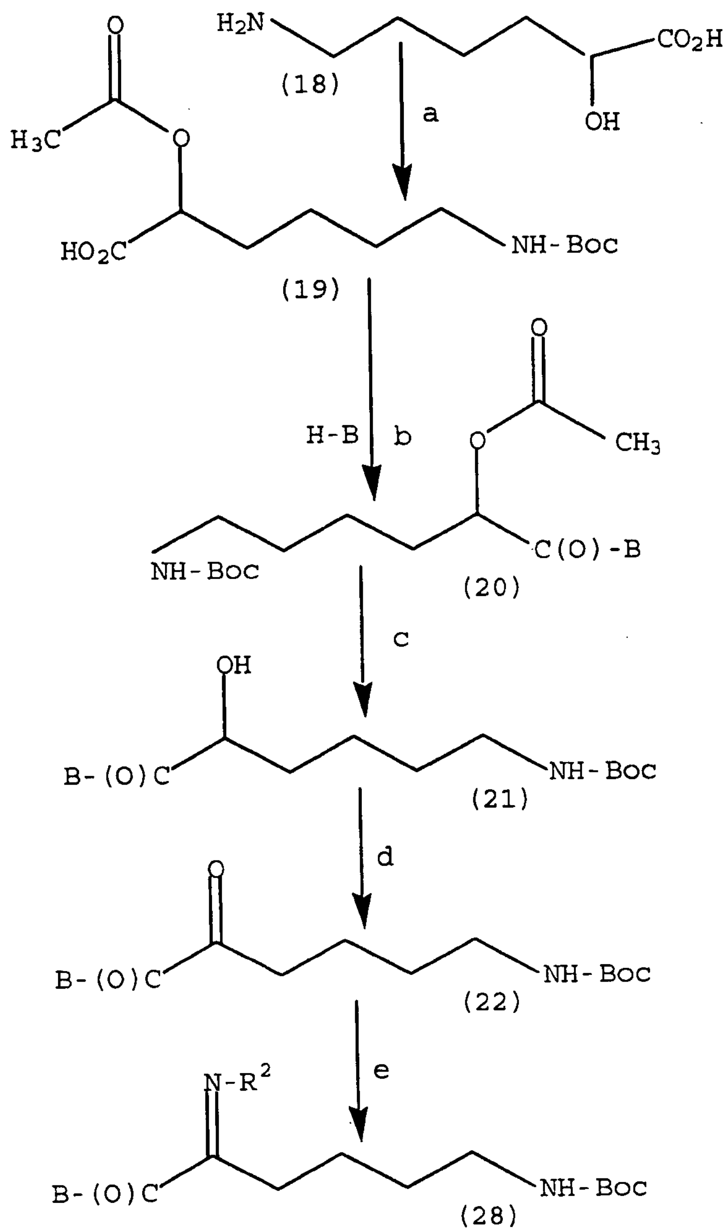
(a) 1. t-butoxycarbonylazide, H_2O, dioxane, MgO
2. acetic anhydride, TEA (b) BOP, DIPEA, DMF
(c) 1 equiv. NaOH, ethanol (d) DMSO, DCC, H_3PO_4
(e) R^1-NH_2, ethanol, sodium carbonate

Scheme 8



(R^1 = hydroxyl, sulfhydryl, OR^6 or SR^6) (a) BH_3, THF
(b) Acylation with R^2: a carboxylic acid choride or anhydride, a chloroformate, an isocyanate, a sulfonyl chloride, sulfinyl chloride, phosphonating, or phosphating reagent with standard conditions
(c) HCl, dioxane or trifluoroacetic acid
(d) H_2O, pH 9-10 with (2) or TEA, DMF with (2b)

Scheme 9



(a) 1. t-butoxycarbonylazide, H_2O, dioxane, MgO

2. acetic anhydride, TEA

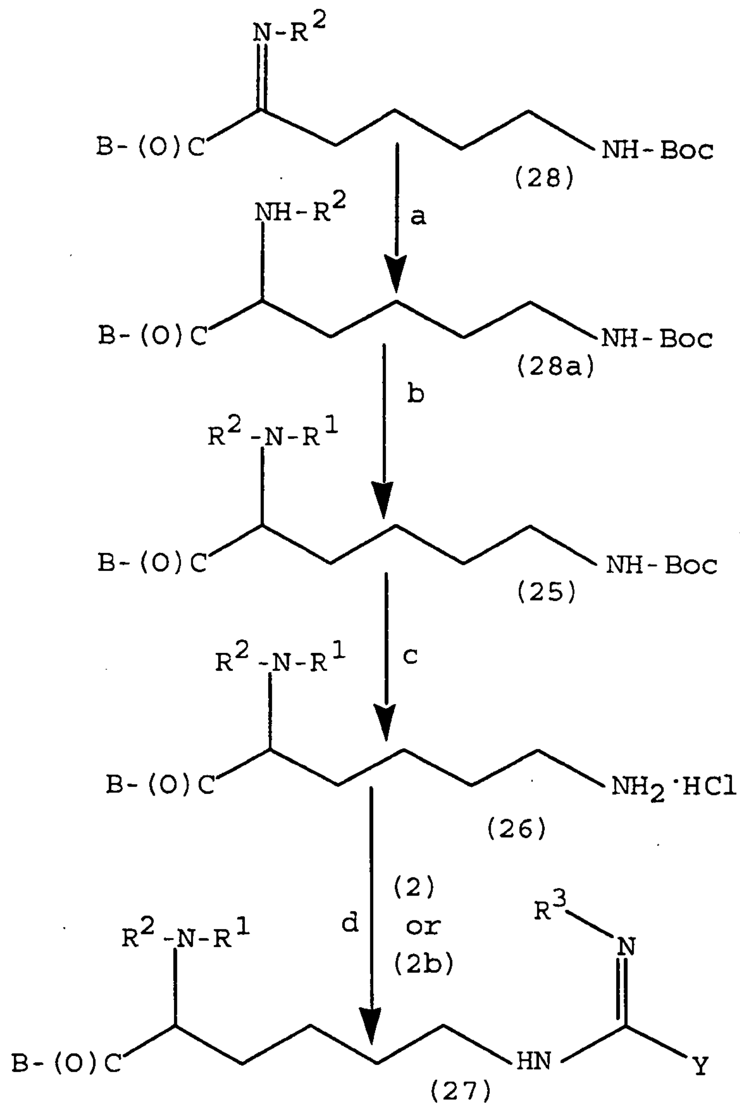
(b) BOP, DIPEA, DMF

(c) 1 equiv. NaOH, ethanol

(d) DMSO, DCC, H_3PO_4

(e) R^2-NH_2 (R^2 = hydroxyl, sulfhydryl, OR^6 or SR^6), ethanol, sodium carbonate

Scheme 10



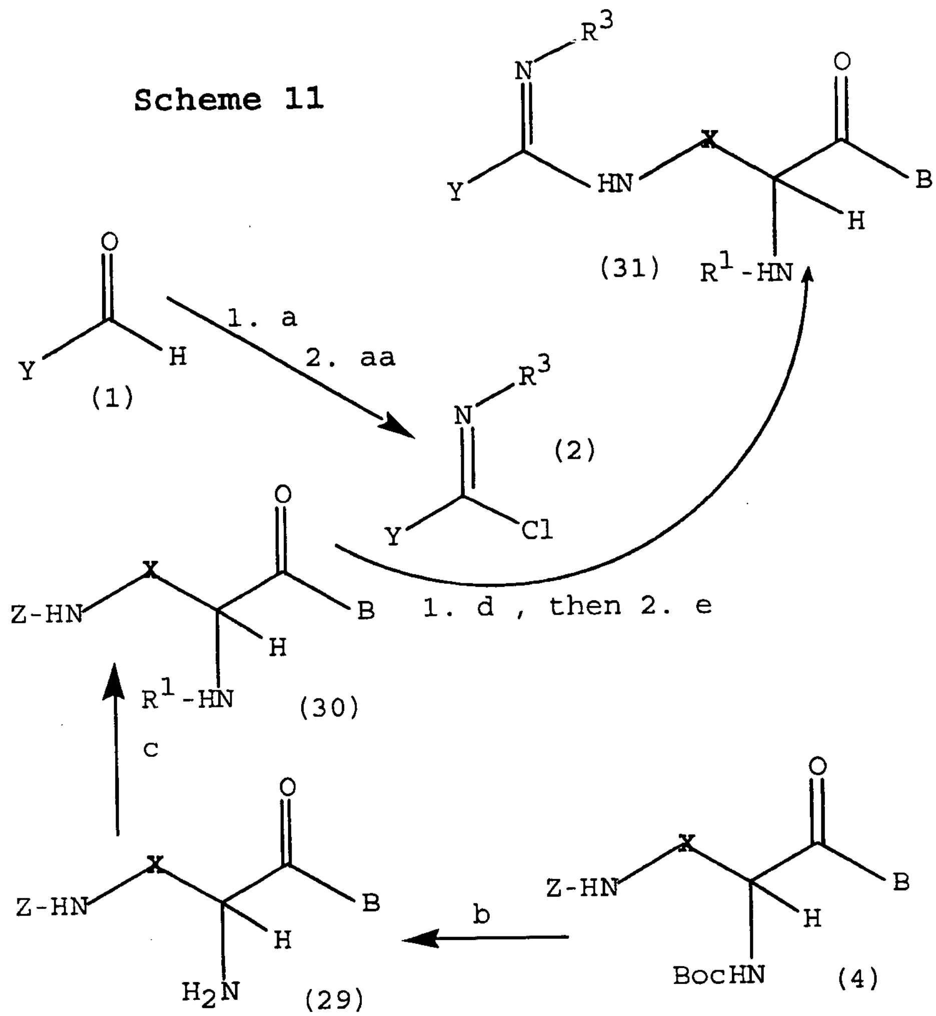
(R^2= hydroxyl, sulfhydryl, OR^6 or SR^6) (a) BH_3, THF

(b) Acylation with R^1: a carboxylic acid choride or anhydride, a chloroformate, an isocyanate, a sulfonyl chloride, sulfinyl chloride, phosphonating, or phosphating reagent with standard conditions

(c) HCl, dioxane or trifluoroacetic acid

(d) H_2O, pH 9-10 with (2) or TEA, DMF with (2b)

Scheme 11



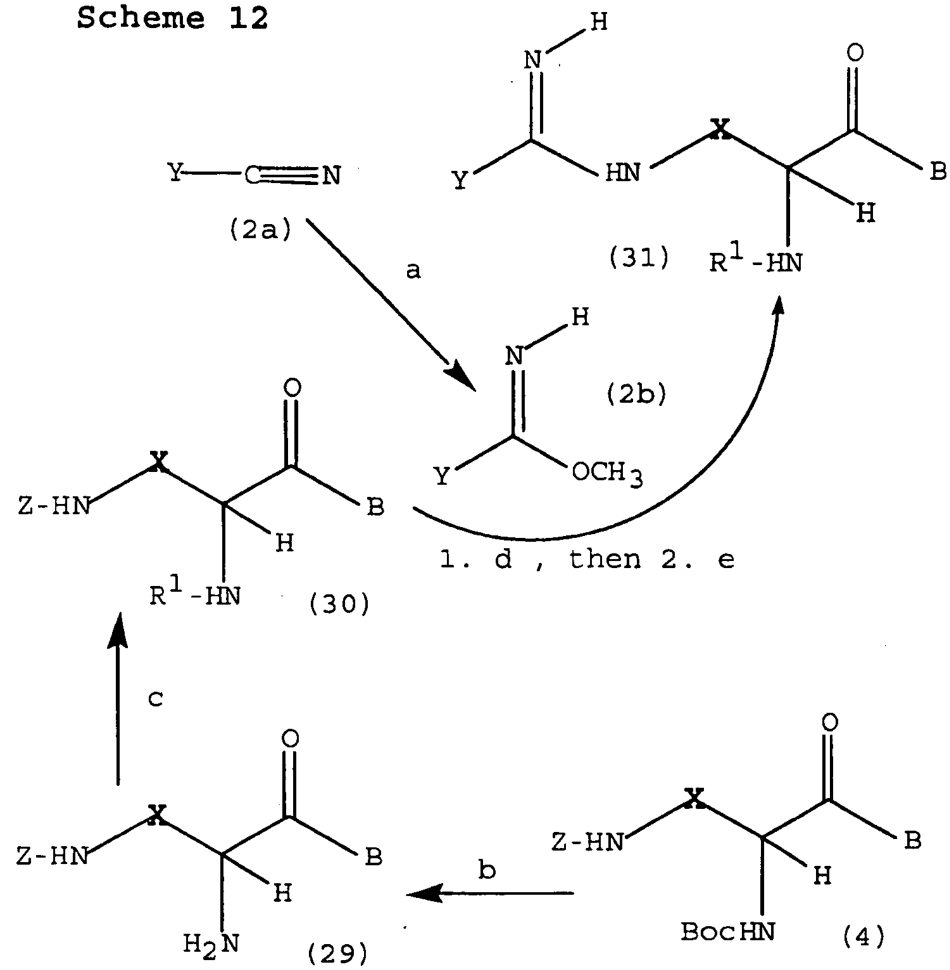
(a) R_3-NH_2 (aa) N-chlorosuccimide, DMF

(b) HCl, dioxane or trifluoroacetic acid

(c) Acylation with R^1: a carboxylic acid choride or anhydride, a chloroformate, an isocyanate, a sulfonyl chloride, sulfinyl chloride, phosphonating, or phosphating reagent with standard conditions

(d) Pd, H_2, Ethanol/Acetic Acid (e) H_2O, pH 9-10

Scheme 12



(a) HCl, Methanol

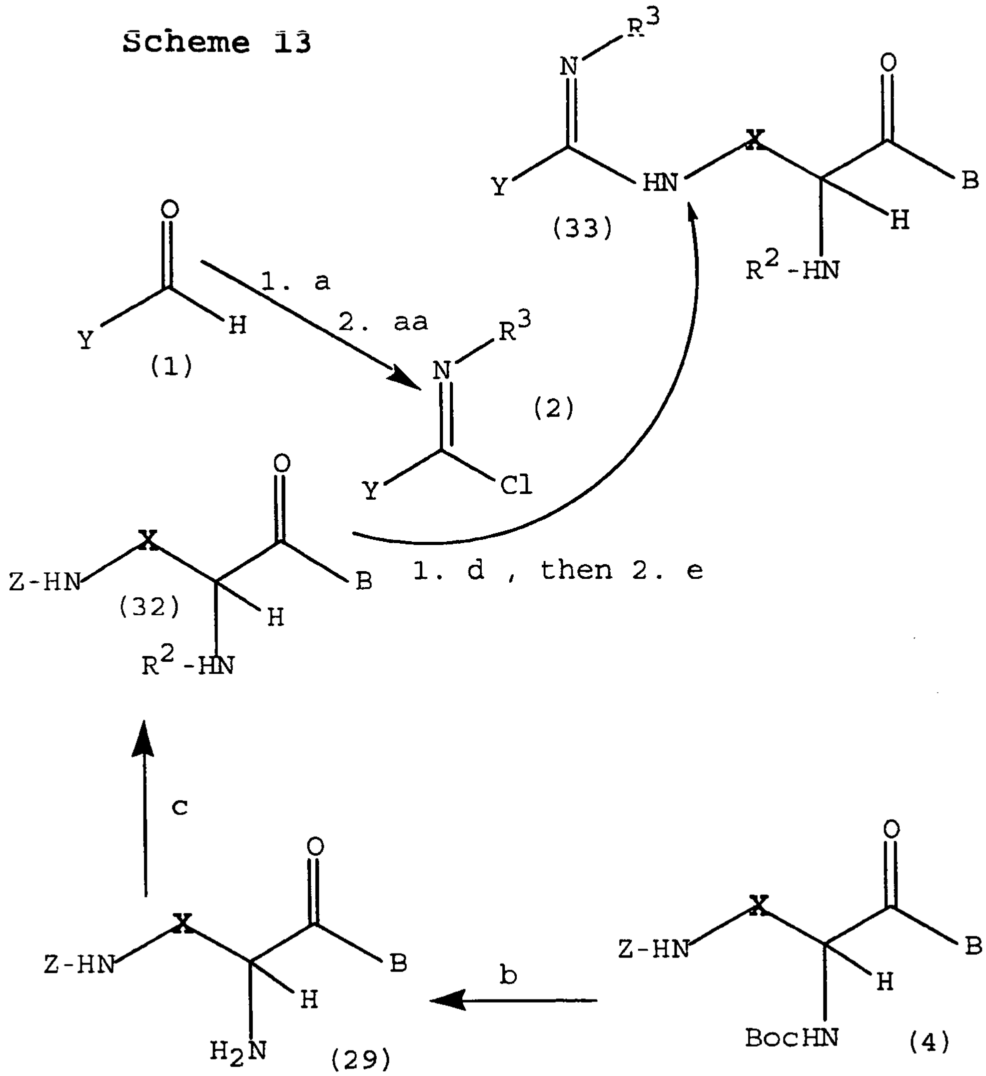
(b) HCl, dioxane or trifluoroacetic acid

(c) Acylation with R^1: a carboxylic acid choride or anhydride, a chloroformate, an isocyanate, a sulfonyl chloride, sulfinyl chloride, phosphonating, or phosphating reagent with standard conditions

(d) Pd, H_2, Ethanol/Acetic Acid

(e) TEA, DMF

Scheme 13



(a) R_3-NH_2 (aa) N-chlorosuccimide, DMF

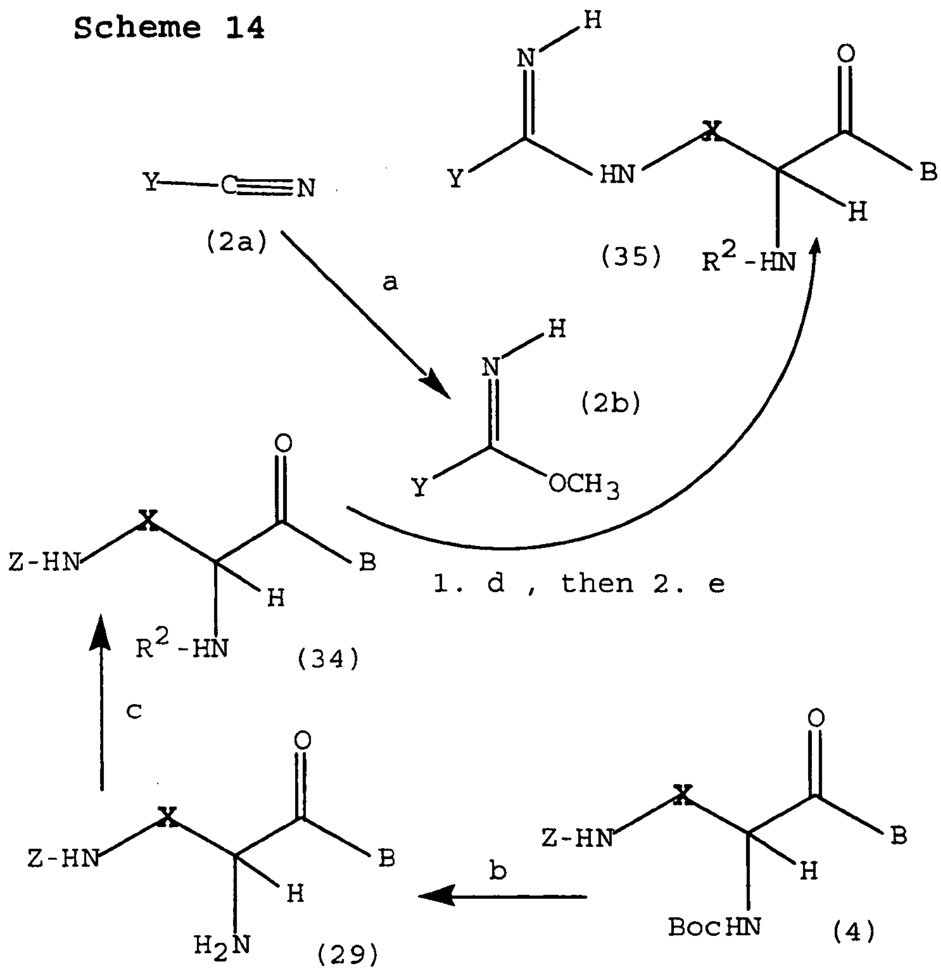
(b) HCl, dioxane or trifluoroacetic acid

(c) Acylation with R^2: a carboxylic acid choride or anhydride, a chloroformate, an isocyanate, a sulfonyl chloride, sulfinyl chloride, phosphonating, or phosphating reagent with standard conditions

(d) Pd, H_2, Ethanol/Acetic Acid

(e) H_2O, pH 9-10

Scheme 14



(a) HCl, Methanol

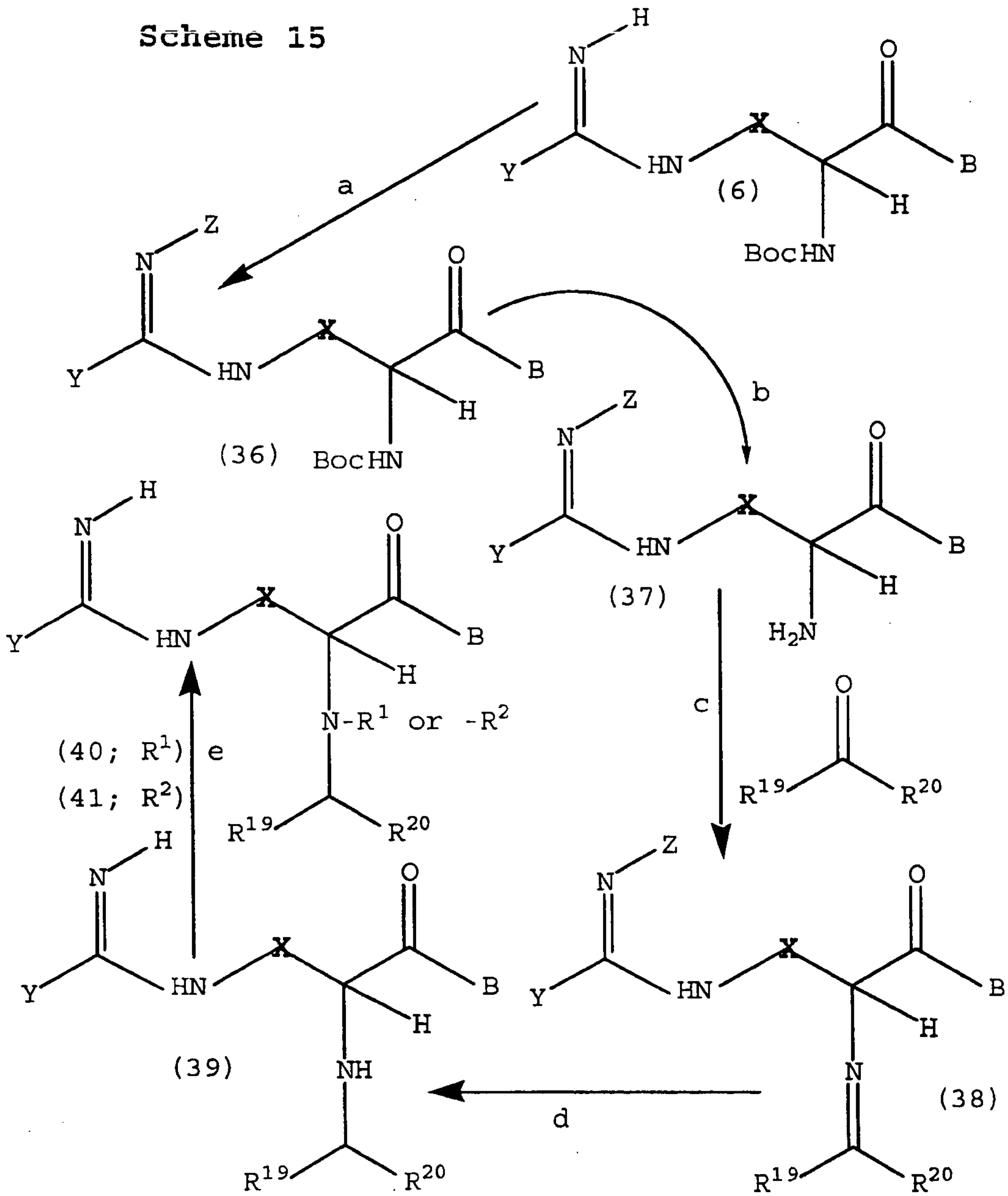
(b) HCl, dioxane or trifluoroacetic acid

(c) Acylation with R^2: a carboxylic acid choride or anhydride, a chloroformate, an isocyanate, a sulfonyl chloride, sulfinyl chloride, phosphonating, or phosphating reagent with standard conditions

(d) Pd, H_2, Ethanol/Acetic Acid

(e) TEA, DMF

Scheme 15



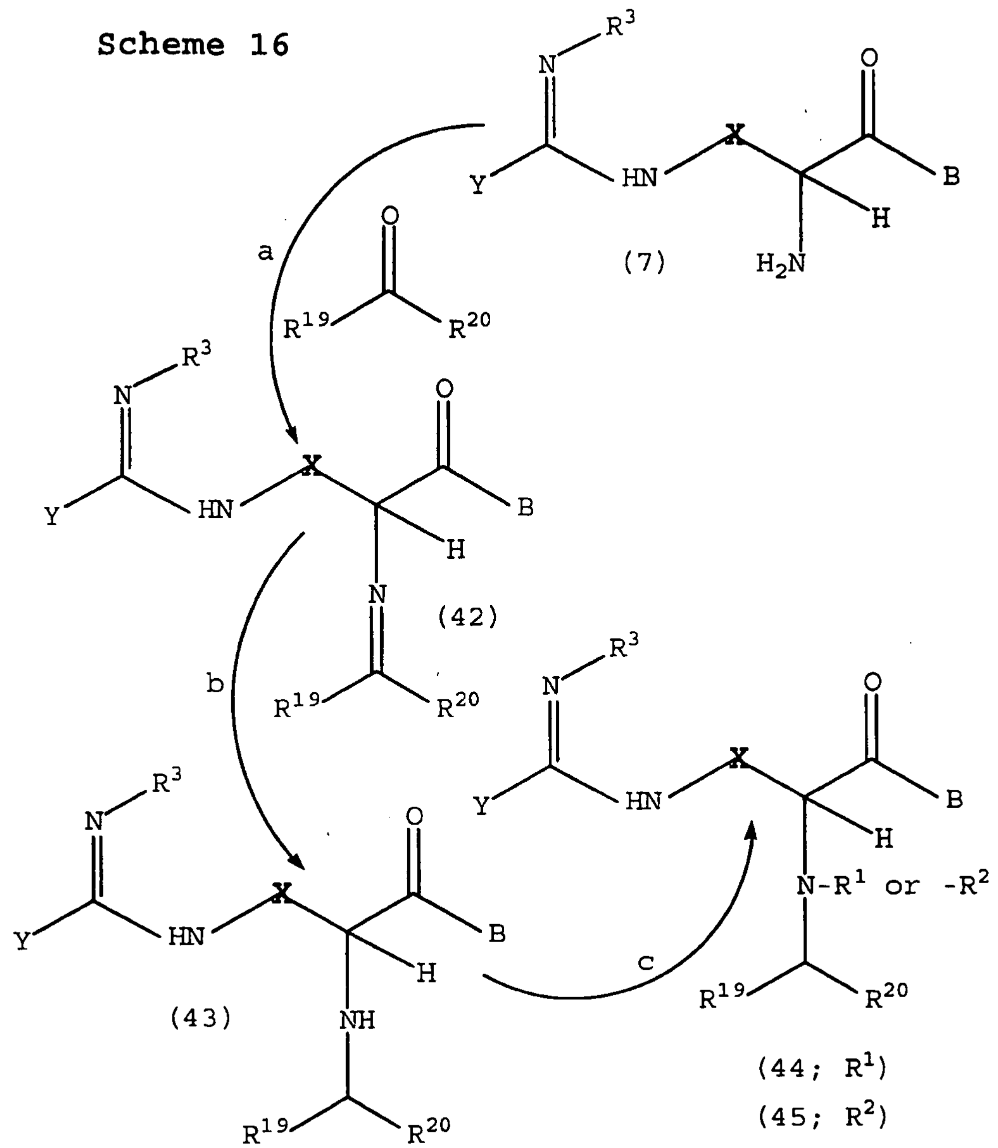
(a) Benzyl chloroformate, Na_2CO_3, THF, Water

(b) HCl, dioxane or trifluoroacetic acid

(c) catalytic p-TsOH, hexane or toluene, azeotropic distillation (d) Pd, H_2, Ethanol/Acetic Acid

(e) Acylation with R^1 or R^2: carboxylic acid choride or anhydride, chloroformate, isocyanate, sulfonyl chloride or sulfinyl chloride with standard conditions.

Scheme 16

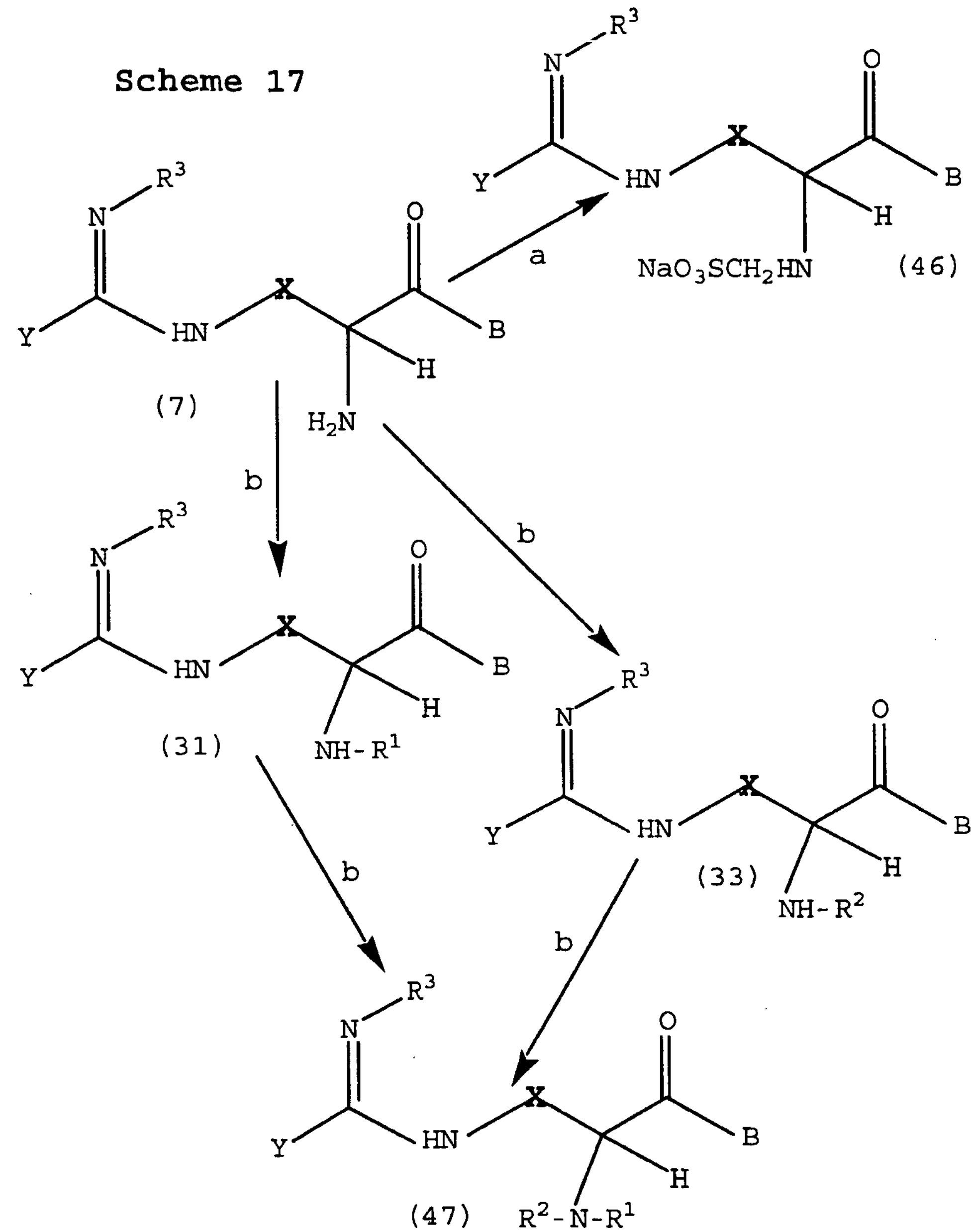


(a) catalytic p-TsOH, hexane or toluene, azeotropic distillation

(b) Pd, H_2, Ethanol/Acetic Acid

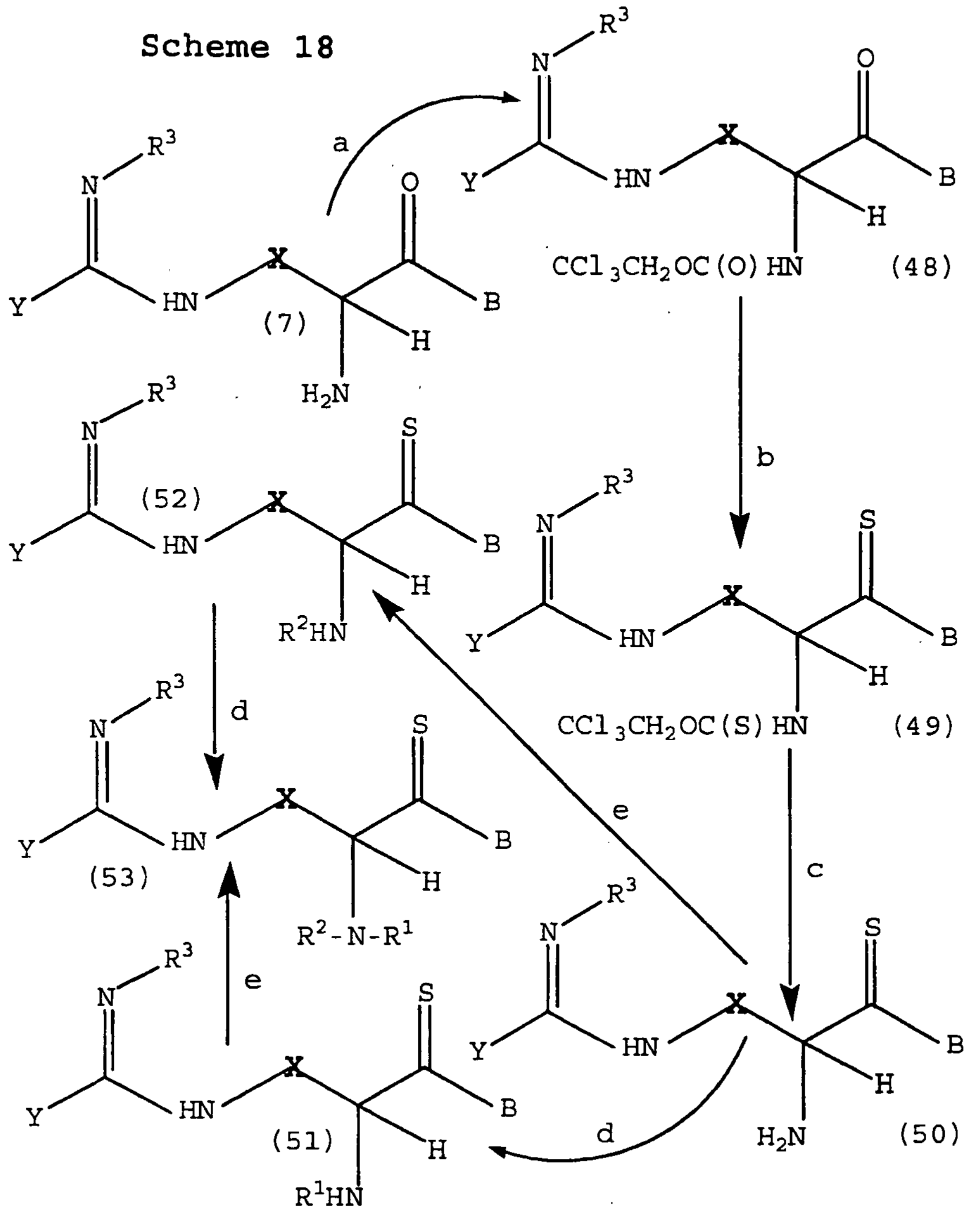
(c) Acylation with R^1or R^2: carboxylic acid choride or anhydride, chloroformate, isocyanate, sulfonyl chloride or sulfinyl chloride with standard conditions.

Scheme 17



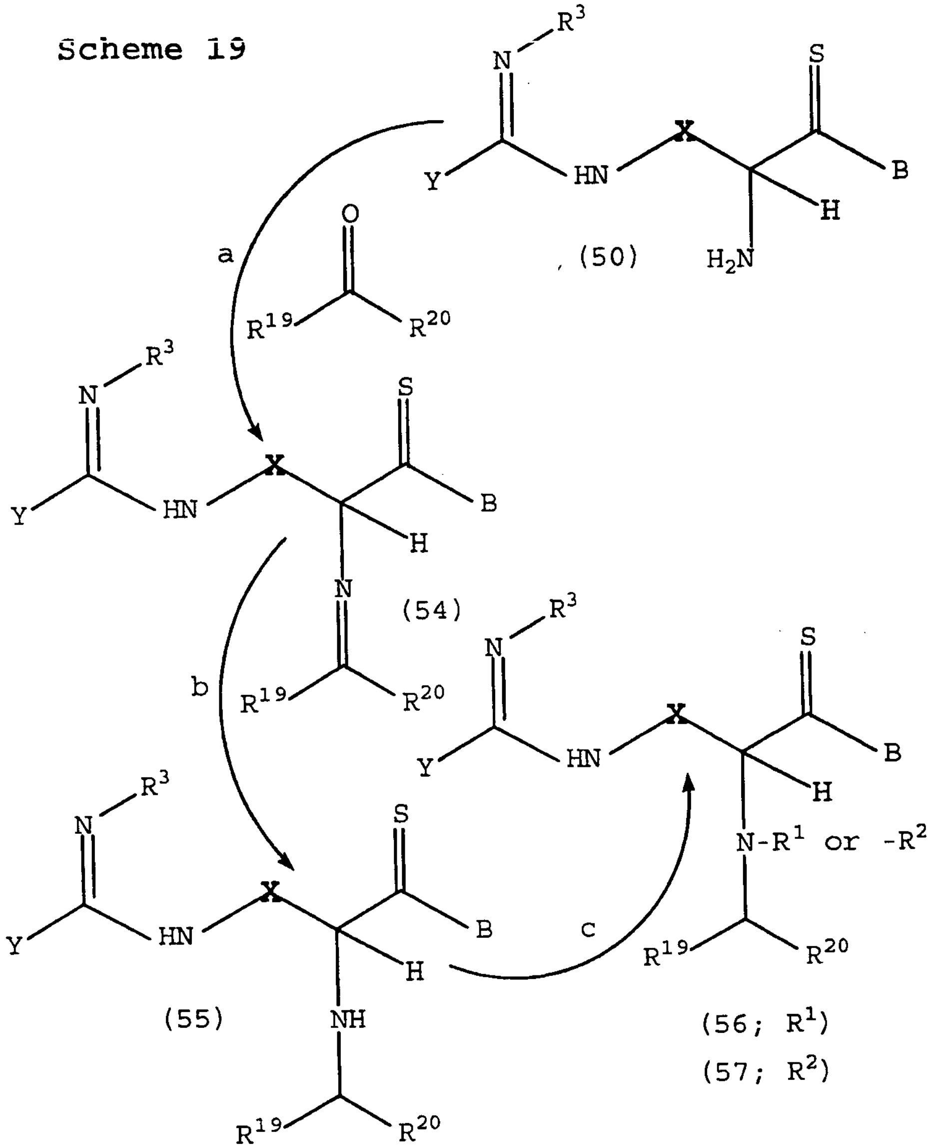
(a) NaO_3SCH_2OH, pH 10-11 [see L. Maier, Phosphorus, Sulfur Silicon Related Elements (1990), 47, 43-46]
(b) 1. Aldehyde, acetal with trace of acid, or ketone, methanol or ethanol, 2. NaCNBH3, methanol, KOH [see R. F. Borch, Organic Synthesis, 52, 124 (1972)

Scheme 18



(a) Trichloroethyl chloroformate, Na_2CO_3, H_2O, THF [see D. Gravel et al., Canadian Journal of Chemistry, 50, 3846(1972] (b) Lawesson's Reagent, [Jones and Bradshaw, Chem.Reviews (1984), 84, 17-30 and cited references.
(c) 1. Zinc dust, Acetic Acid, 2. Na_2CO_3, H_2O
(d) Acylation with R^1: carboxylic acid choride or anhydride, chloroformate, isocyanate, sulfonyl chloride, or sulfinyl chloride with standard conditions
(e) Acylation with R^2 with (d)-conditions.

Scheme 19

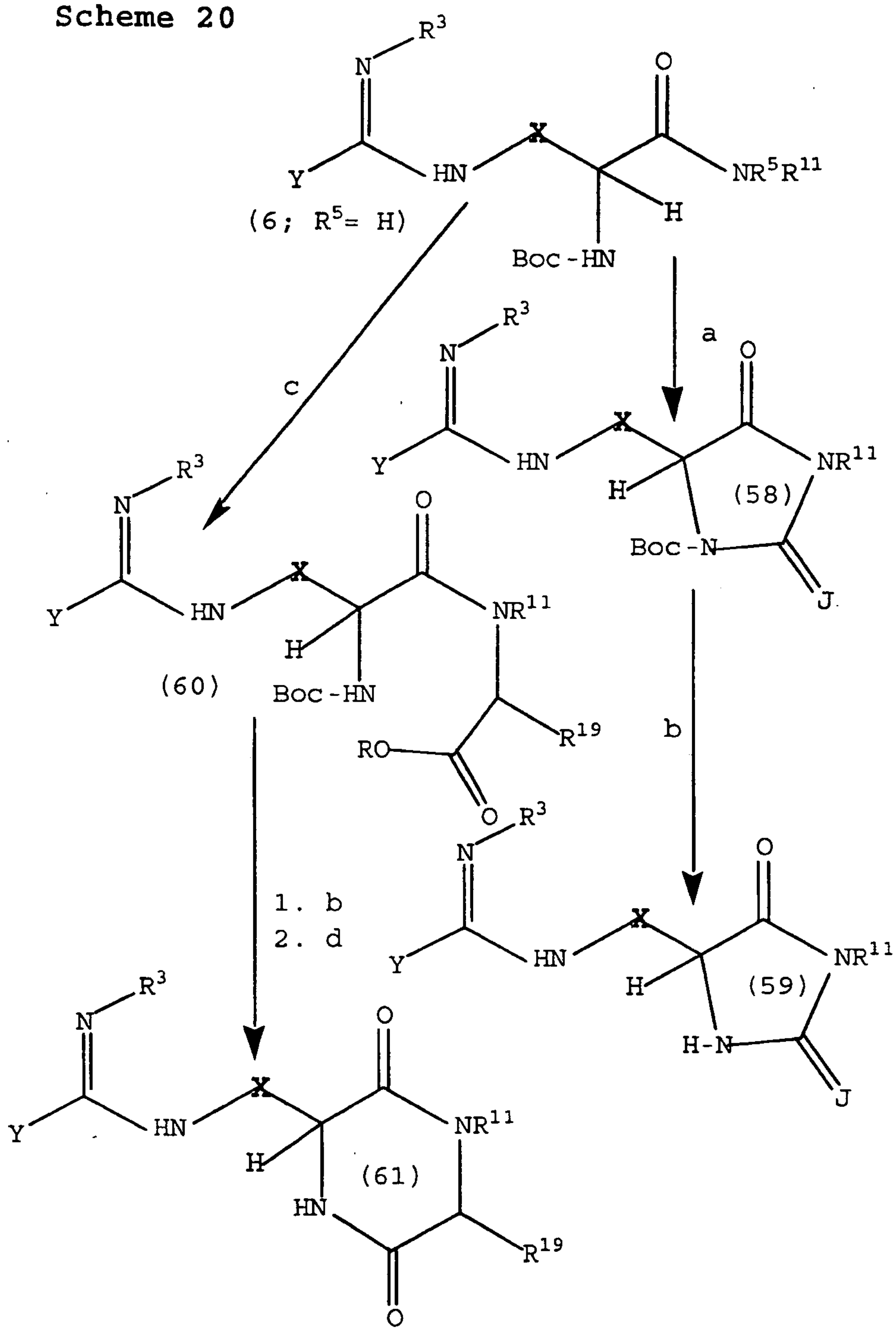


(a) catalytic p-TsOH, hexane or toluene, azeotropic distillation

(b) $NaCNBH_3$, methanol, KOH [see R. F. Borch, Organic Synthesis, 52, 124 (1972)

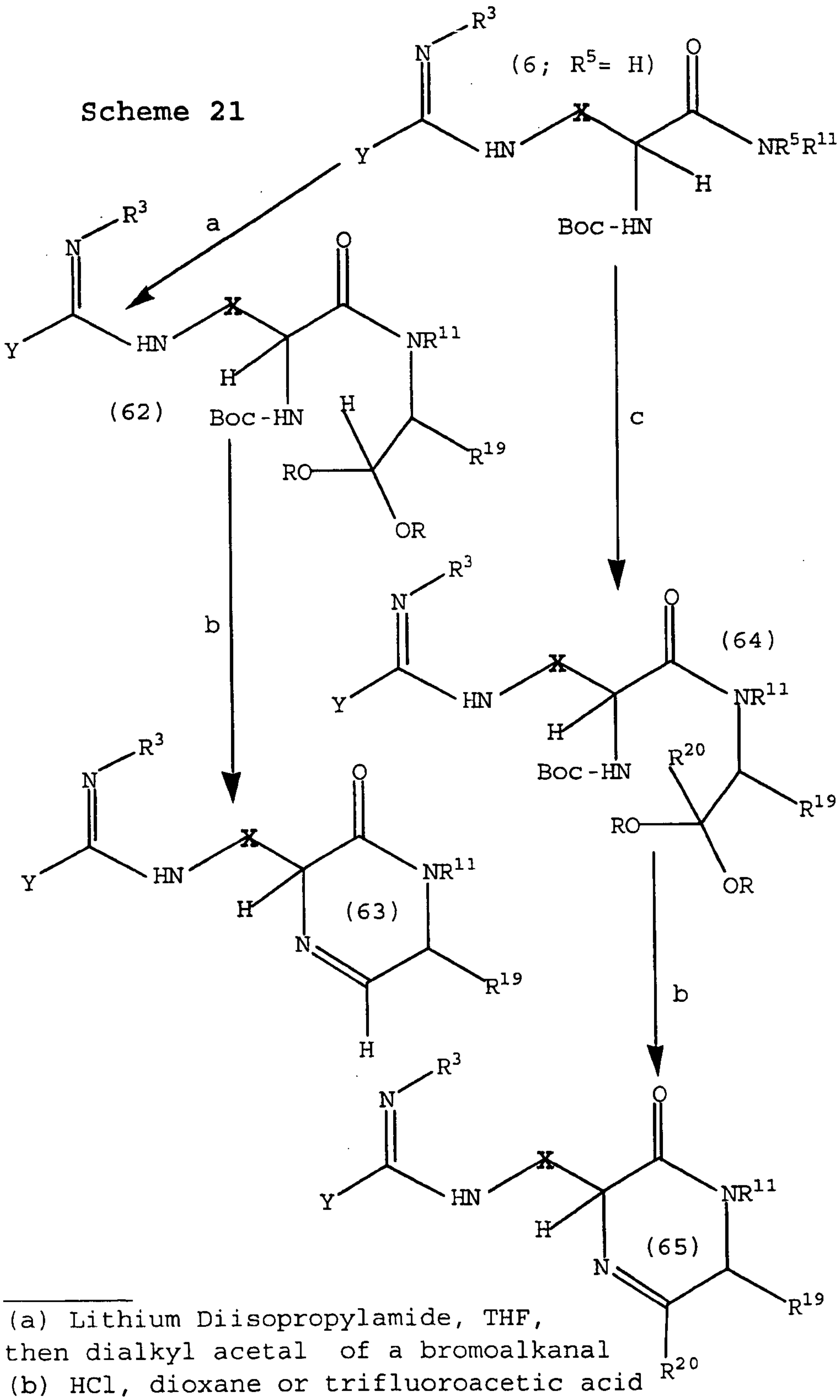
(c) Acylation with R^1or R^2: carboxylic acid choride or anhydride, chloroformate, isocyanate, sulfonyl chloride, or sulfinyl chloride with standard conditions.

Scheme 20



(a) 2 equivalents of Lithium Diisopropylamide, THF, $C(O)Cl_2$ or $C(S)Cl_2$
(b) HCl, dioxane or trifluoroacetic acid
(c) 1. Lithium Diisopropylamide, THF,
2. 2-haloalkanoate ester (R)
(d) Na_2CO_3, toluene, heat

Scheme 21

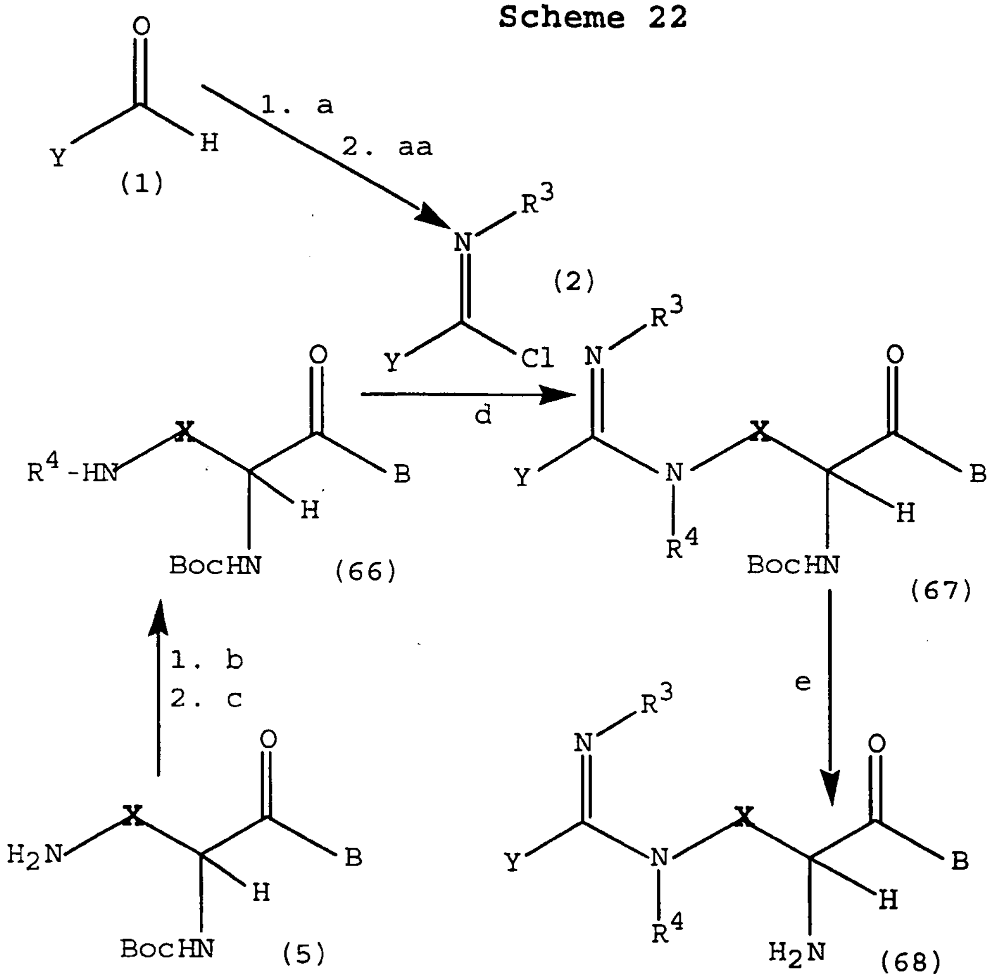


(a) Lithium Diisopropylamide, THF, then dialkyl acetal of a bromoalkanal

(b) HCl, dioxane or trifluoroacetic acid

(c) Lithium Diisopropylamide, THF, then dialkyl acetal of a bromoalkanone

Scheme 22



(a) R_3-NH_2 (aa) N-chlorosuccimide, DMF

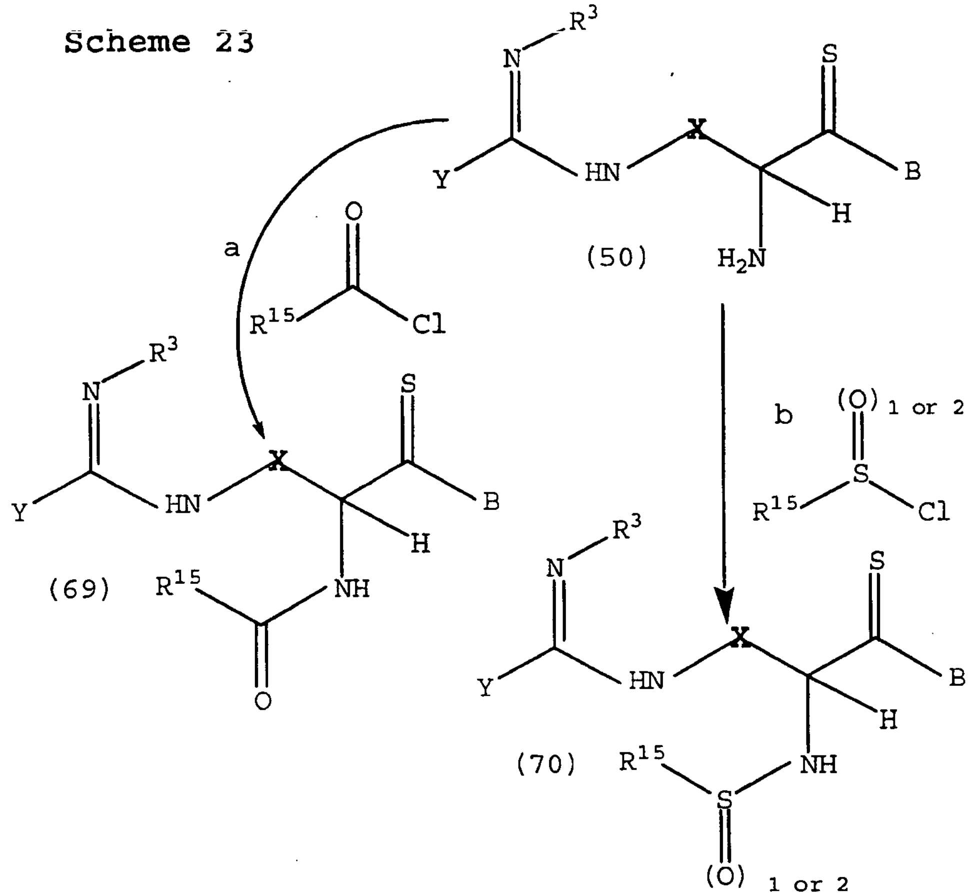
(b) An aldehyde or ketone precursor to R^4, catalytic p-TsOH, hexane or toluene, azeotropic distillation

(c) $NaCNBH_3$, methanol, KOH [see R. F. Borch, Organic Synthesis, 52, 124 (1972)]

(d) H_2O, pH 9-10

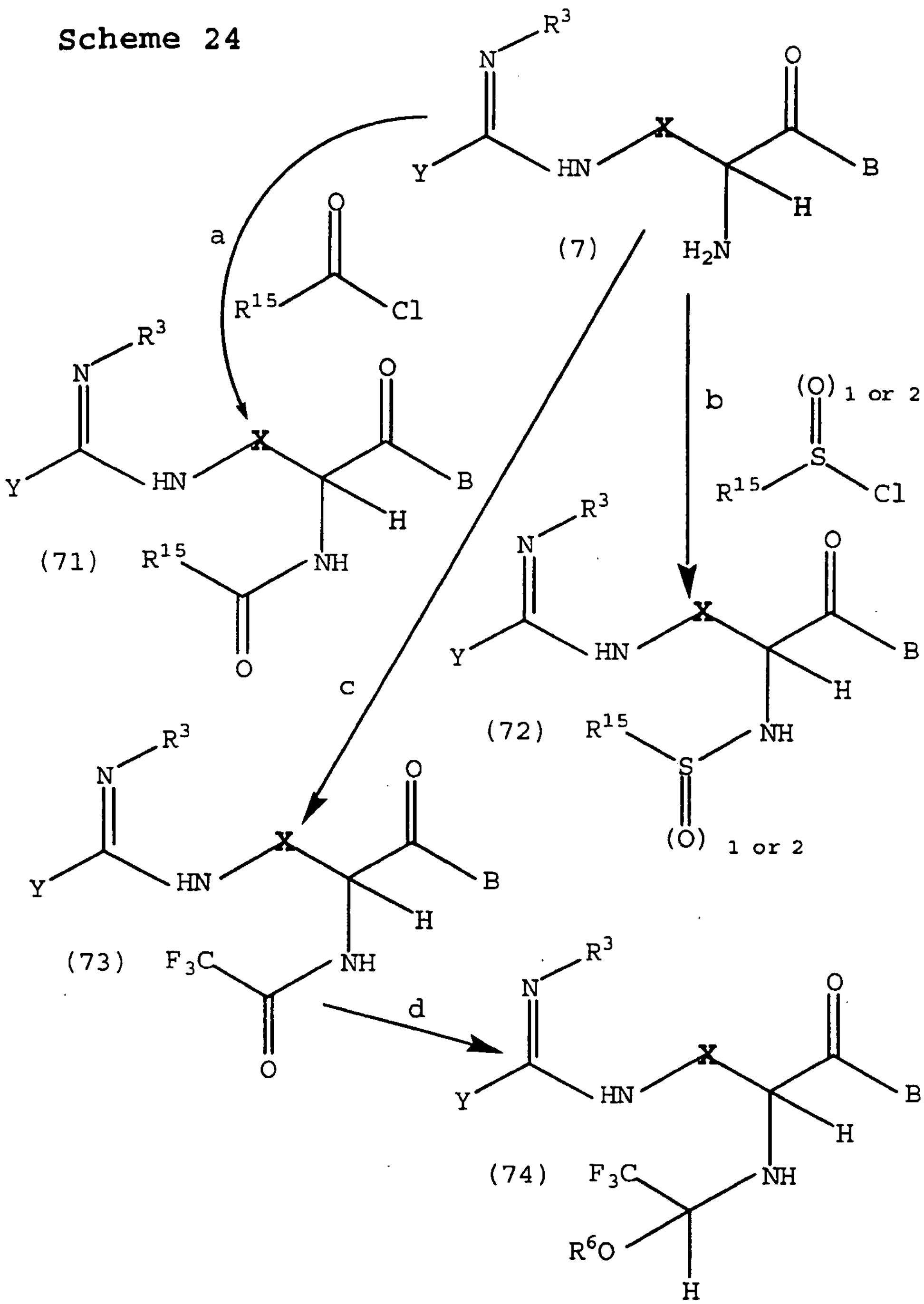
(e) HCl, dioxane or trifluoroacetic acid

Scheme 23



(a) Na_2CO_3, aqueous dioxane; Acylation with a carboxylic acid choride or anhydride
(b) Na_2CO_3, aqueous dioxane; sulfonation with a sulfonyl chloride or sulfinyl chloride with standard conditions

Scheme 24



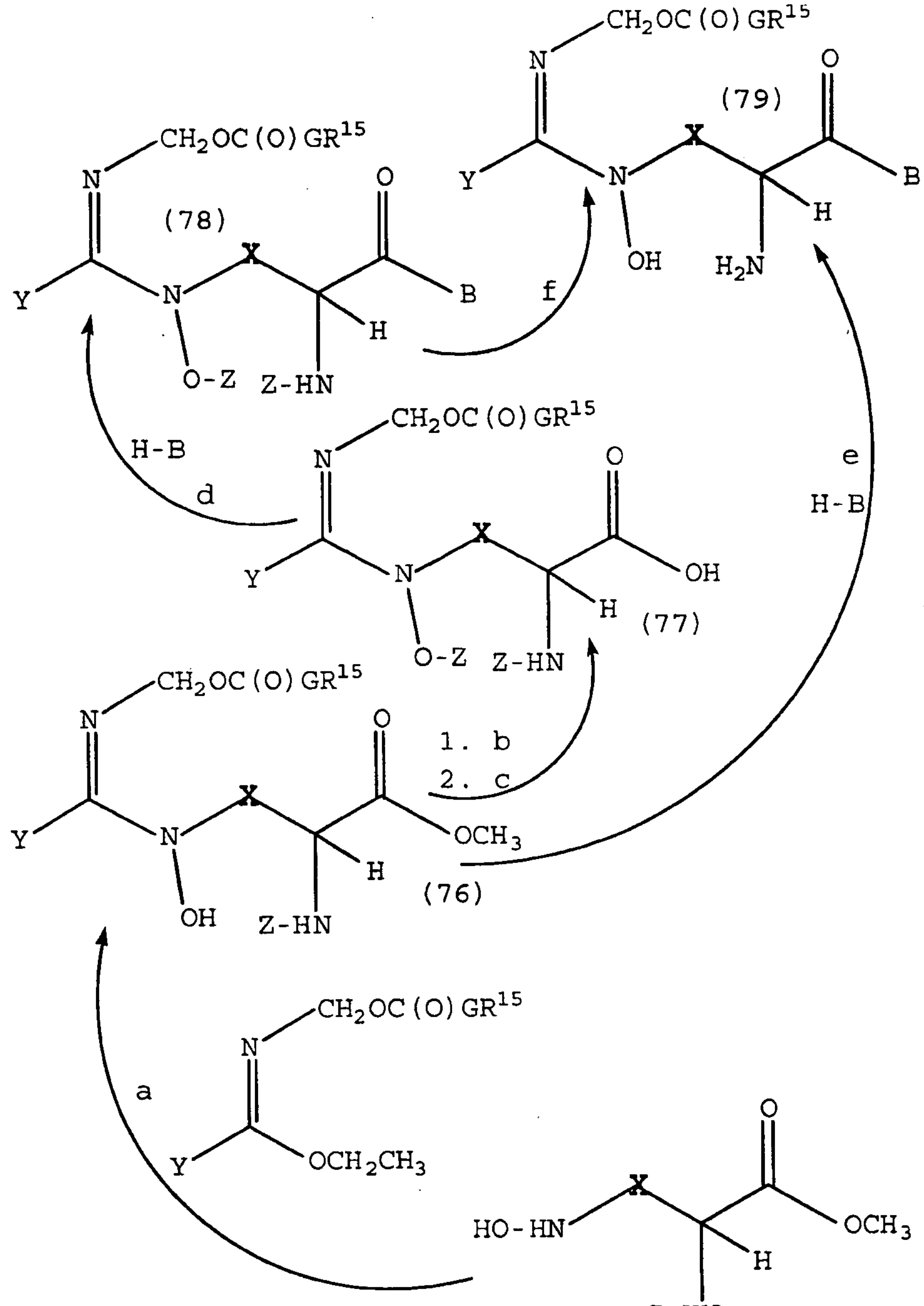
(a) Na_2CO_3, aqueous dioxane; Acylation with carboxylic acid choride or anhydride

(b) Na_2CO_3, aqueous dioxane; sulfonation with sulfonyl chloride or sulfinyl chloride with standard conditions

(c) trifluoroacetic acid anhydride

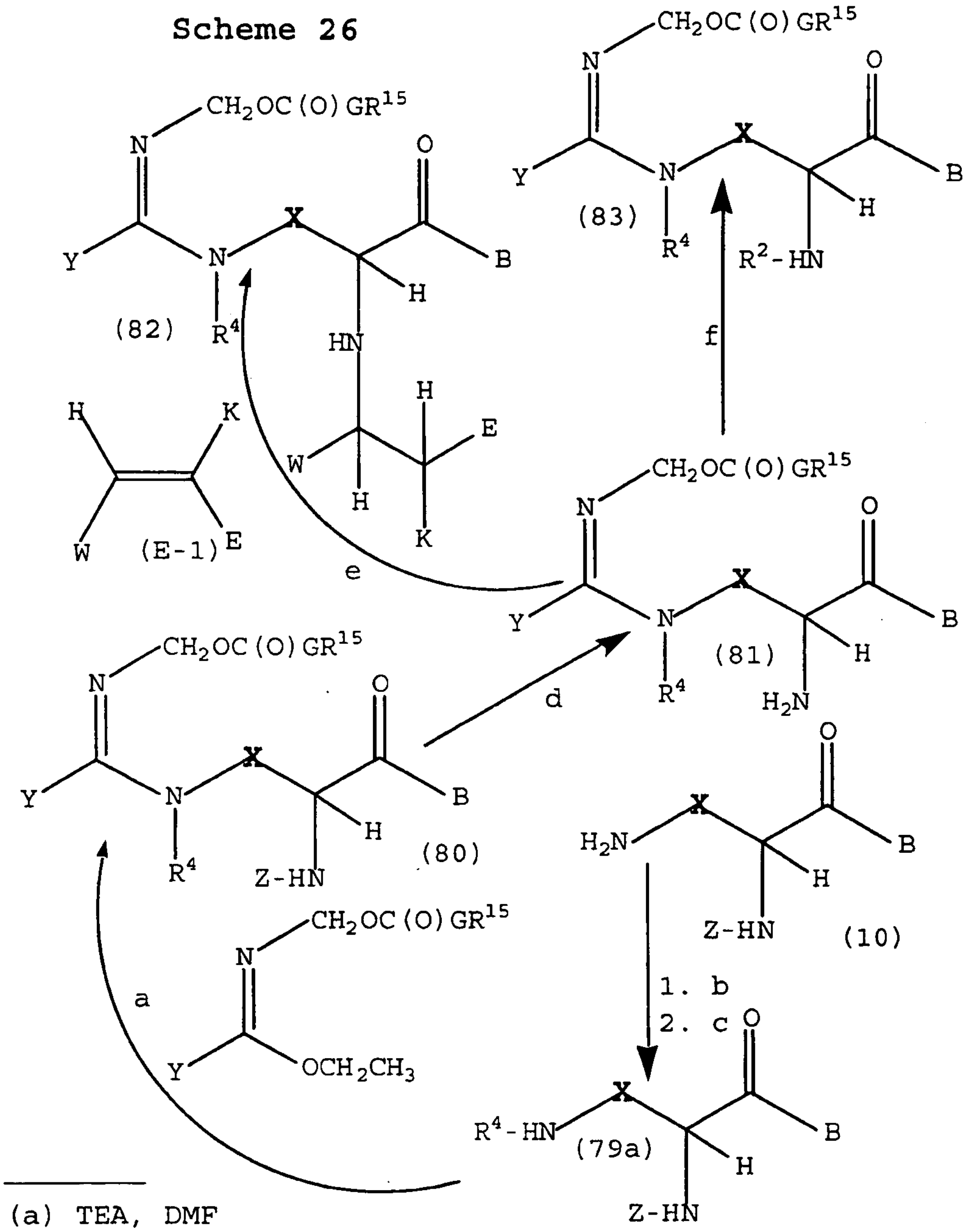
(d) $NaBH_4$, R^6-OH, aprotic polar solvent

Scheme 25



(a) TEA, DMF
(b) benzyl chloroformate, Na_2CO_3, dioxane, water
(c) NaOH, H_2O
(d) BOP, DIPEA, DMF
(e) H-B, DMF, heat
(f) Pd, H_2, Ethanol

Scheme 26



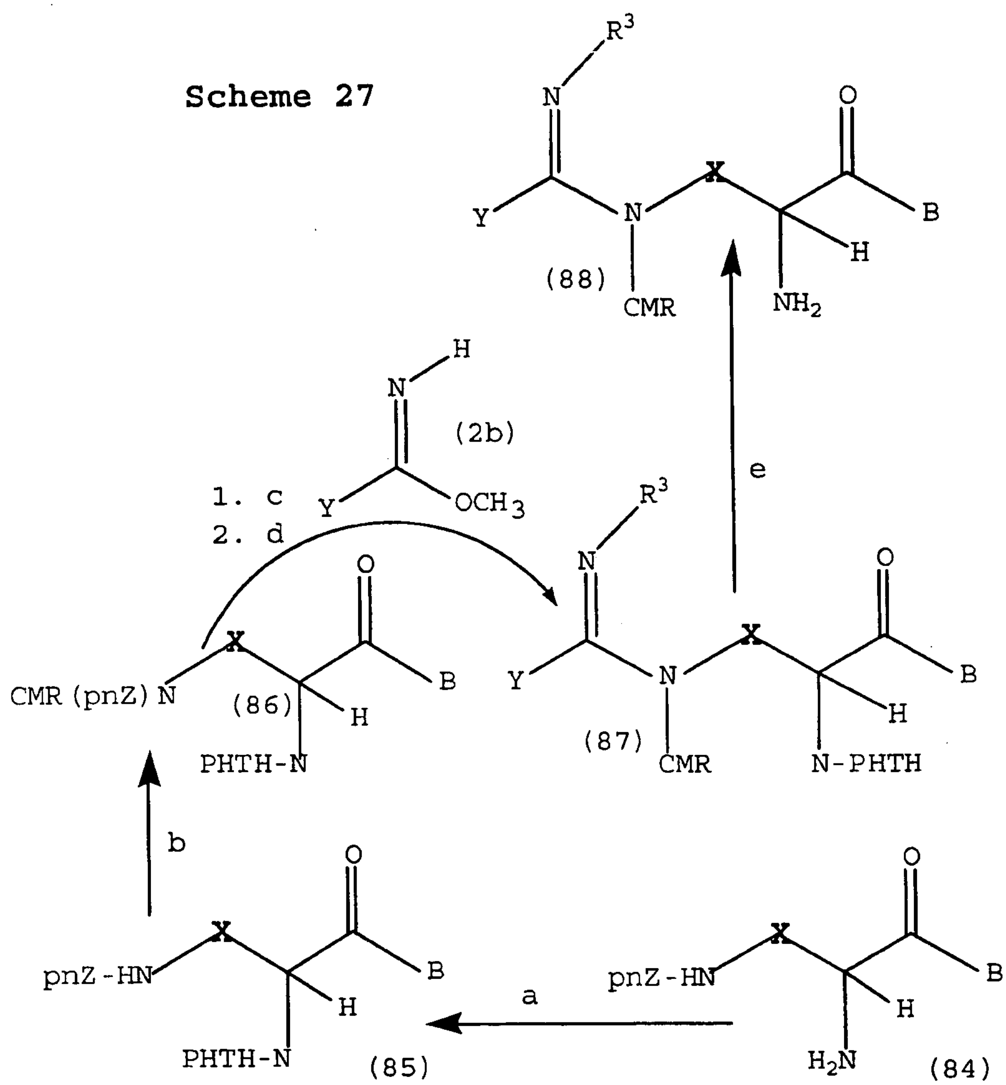
(a) TEA, DMF

(b) an aldehyde or ketone precursor to R^4, catalytic p-TsOH, hexane or toluene, azeotropic distillation

(c) NaCNBH3, methanol, KOH [see R. F. Borch, Organic Synthesis, 52, 124 (1972) (d) Pd, H_2, Ethanol

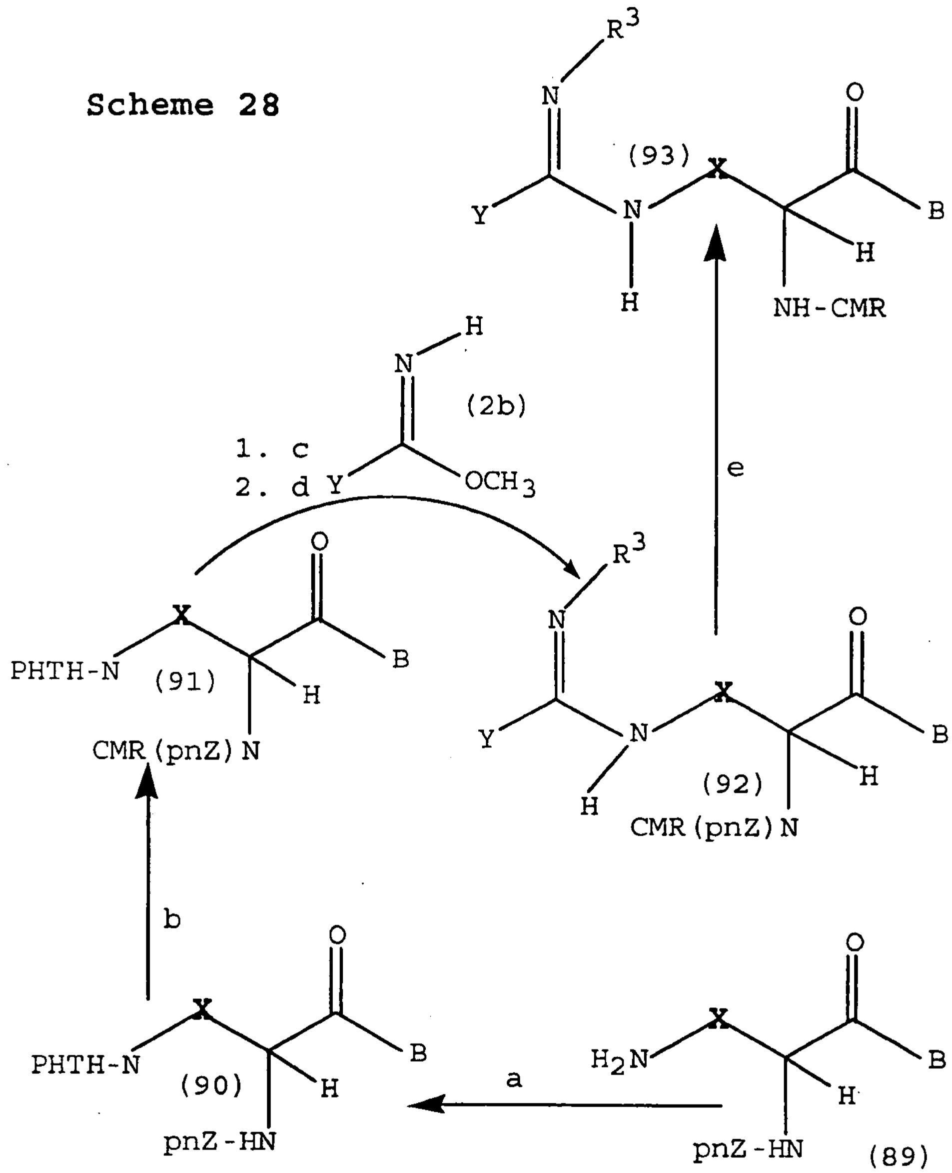
(e) TEA, 0-80 °C (f) Acylation with R^2: carboxylic acid choride or anhydride, chloroformate, isocyanate, sulfonyl chloride,or sulfinyl chloride with standard conditions

Scheme 27



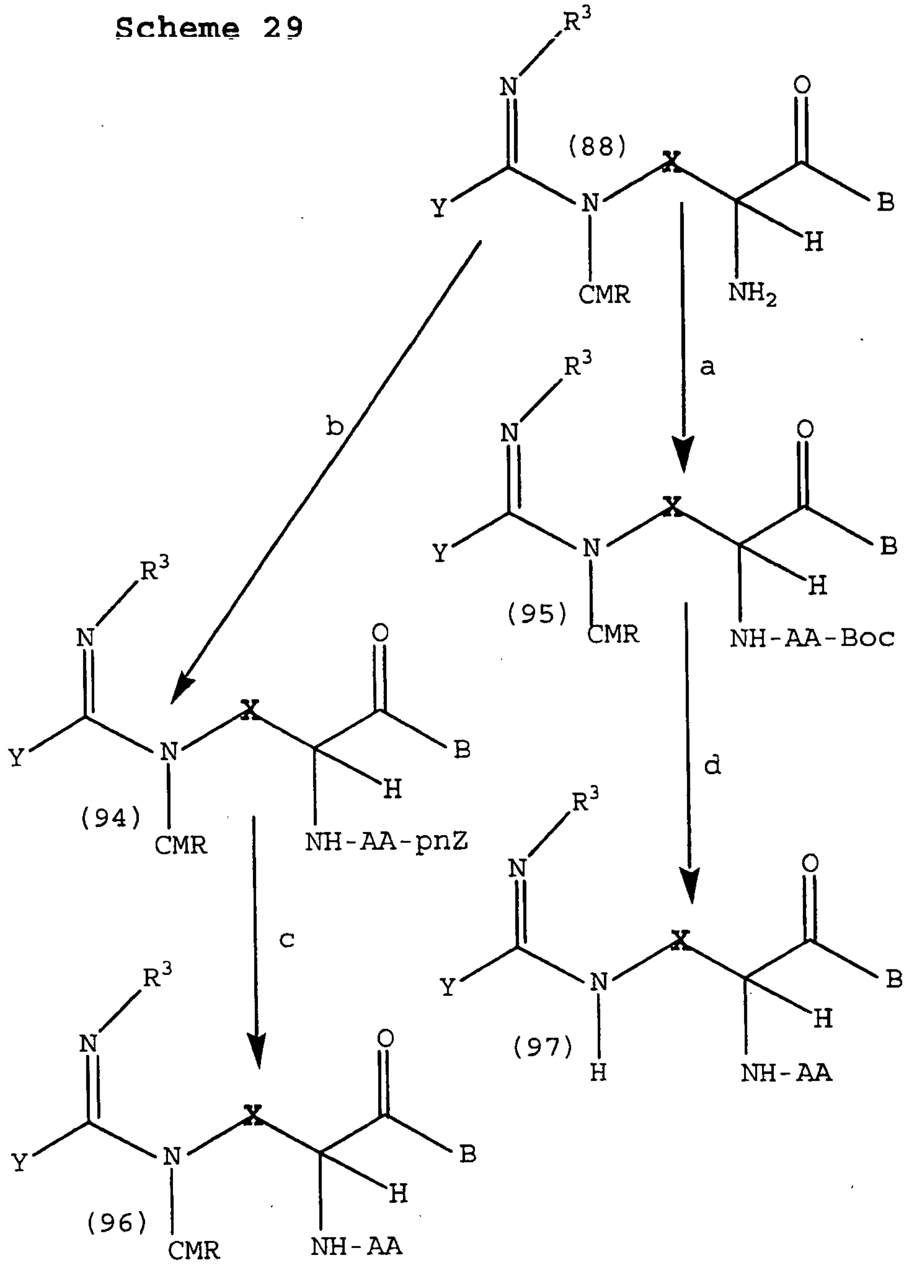
(a) Phthalic anhydride, THF at reflux
(b) LDA, THF, then Alkylation with a chloromethylation reagent (CMR)
(c) Pd, H_2, Ethanol
(d) H_2O, pH 9-10
(e) Hydrazine, methanol, reflux.

Scheme 28



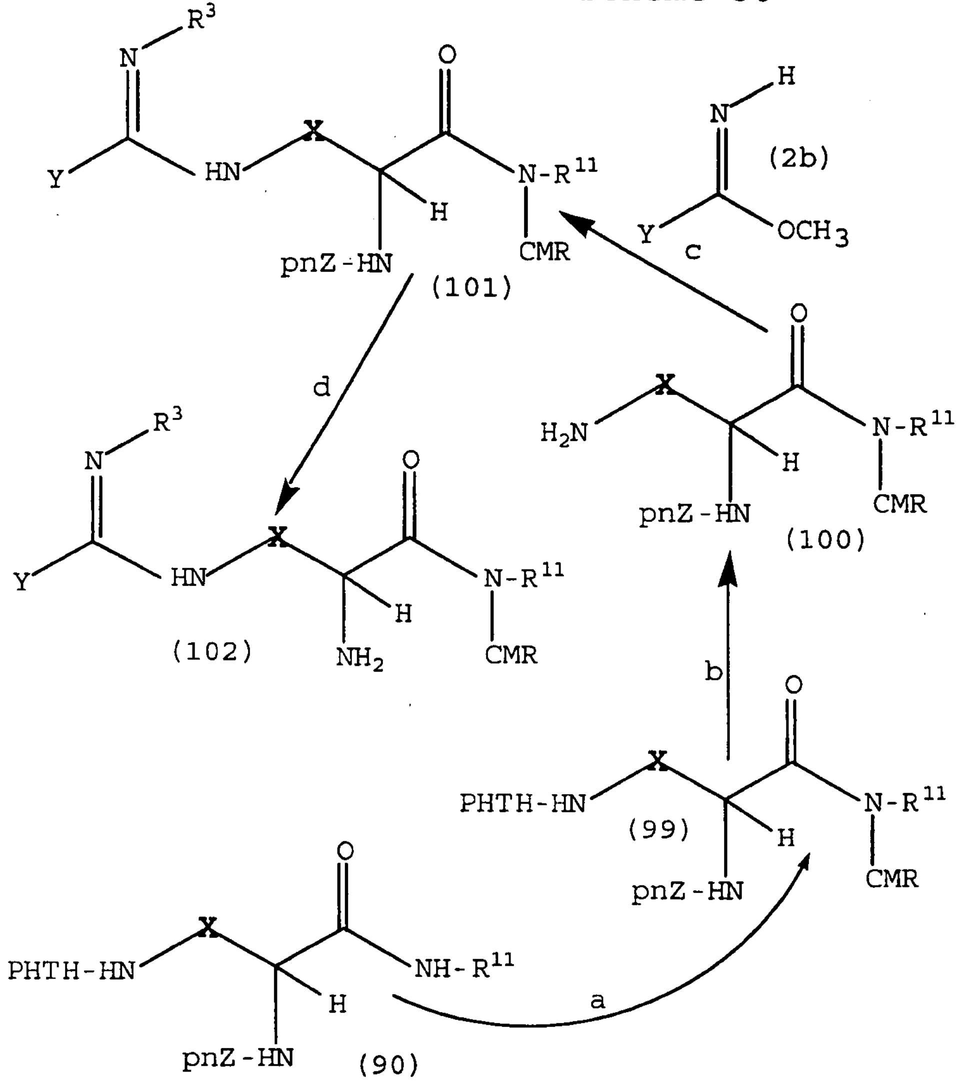
(a) Phthalic anhydride, THF at reflux
(b) LDA, THF Alkylation with a chloromethylation reagent (CMR)
(c) Hydrazine, methanol, reflux
(d) H_2O, pH 9-10
(e) Pd, H_2, Ethanol

Scheme 29



(a) A t-Butoxycarbonyl amino acid (Boc-AA), BOP, DIPEA, DMF
(b) A 4-nitrobenzyloxycarbonyl amino acid (pnZ-AA), BOP, DIPEA, DMF
(c) Pd, H_2, Ethanol
(d) HCl, dioxane, H_2O

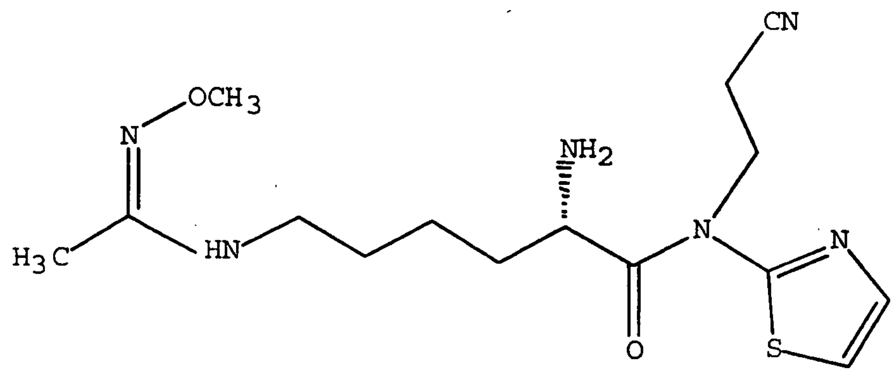
Scheme 30



(a) LDA, THF Alkylation with a chloromethylation reagent (CMR)
(b) Hydrazine, methanol, reflux
(c) H2O, pH 9-10
(d) Pd, H_2, Ethanol

Without further elaboration, it is believed that one skilled in the art can, using the preceding descriptions, utilize the present invention to its fullest extent. Therefore the following preferred specific embodiments are to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever. Compounds containing multiple variations of the structural modifications illustrated in the preceding schemes or the following Examples are also contemplated.

All experiments can be performed under either dry nitrogen or argon. All solvents and reagents can be used without further purification unless otherwise noted. The routine work-up of the reactions involve the addition of the reaction mixture to a mixture of either neutral, acidic, or basic aqueous solutions and organic solvent. The aqueous layer is extracted n times (x) with the indicated organic solvent. The combined organic extracts are washed n times (x) with the indicated aqueous solutions, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and purified as indicated. Separations by column chromatography are achieved with conditions described by Still. (Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatograhic Technique for Preparative Separation with Moderate Resolution. *J. Org. Chem.*, **1978**, *43*, 2923-2925.) The hydrochloride salts are made from 1N HCl, HCl in ethanol (EtOH), 2 N in MeOH, or 6 N HCl in dioxane. Thin layer chromatograms are run on 0.25 mm EM precoated plates of silica gel 60 F254. High performance liquid chromatograms (HPLC) are obtained from C-8 or C-18 reverse phase columns which are obtained from several vendors. Analytical samples are dried in an Abderhalden apparatus at either 56°C or 78°C. ^1H NMR spectra can be obtained from either General Electric QE-300 or Varian VXR 400 MHz spectrometer. ^{13}C NMR spectra are obtained from a Varian spectrometer at 125.8 MHz.



EXAMPLE 1

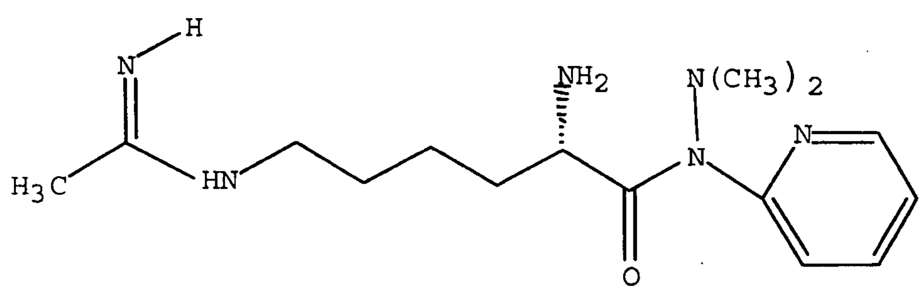
Ex-1a) To a stirring DMF solution of e-Z-a-Boc-L-Lysine (3.80 g, 10.0 mmol), N-(2-cyanoethyl)-2-aminothiazole (1.46 g, 10.5 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl]ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-(2-cyanoethyl)-N-(2-thiazolyl)-e-Z-a-Boc-L-Lysinamide.

Ex-1b) N-(2-cyanoethyl)-N-(2-thiazolyl)-e-Z-a-Boc-L-Lysinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product N-(2-cyanoethyl)-N-(2-thiazolyl)-a-Boc-L-Lysinamide.

Ex-1c) To a 125 mL flask is added 2.46 g (0.01 mol) of N-(2-cyanoethyl)-N-(2-thiazolyl)-a-Boc-L-Lysinamide and 70mL of water. This solution is adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 2.15 g of O-methyl chloroacetaldoxime which is prepared immediately prior to use by the reaction of 5.38 g (0.05 mol) of O-methyl acetaldoxime with 8 g (0.060 mol) of N-chlorosuccinimide in 65 mL of N,N-dimethylformamide at 0°C. The O-methyl chloroacetaldoxime is isolated after three hours by extracting into diethyl ether and washing with aqueous NaCl. Drying with $MgSO_4$, filtration and concentration

under 30°C affords the O-methyl chloroacetaldoxime as a pale yellow oil. During the O-methyl chloroacetaldoxime addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The Boc-protected product is then eluted with 10% aqueous pyridine.

After concentrating, the product produced in **Ex-1c** is deprotected by allowing it to stand in 2N HCl at 25°C for two hours. Concentrating in vacuo afforded L-N-(2-cyanoethyl)-N-(2-thiazolyl)- e-N (methoxyiminoethyl)lysinamide dihydrochloride.



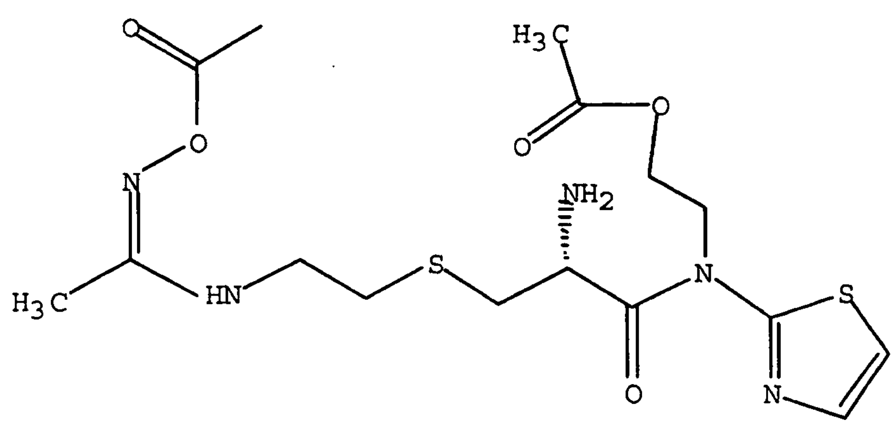
EXAMPLE 2

Ex-2a) To a stirring DMF solution of e-Z-a-Boc-L-Lysine (3.80 g, 10.0 mmol), N,N-dimethyl-N'-(2-pyridyl)hydrazine dihydrochloride (2.31 g, 10.5 mmol), 2.53 g triethylamine (0.025 mol) and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl]ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-(2-dimethylamino)-N-(2-pyridyl)-e-Z-a-Boc-L-Lysinamide.

Ex-2b) N-(2-dimethylamino)-N-(2-pyridyl)-e-Z-a-Boc-L-Lysinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product N-(2-dimethylamino)-N-(2-pyridyl)-a-Boc-L-Lysinamide.

Ex-2c) To a 125 mL flask is added 2.46 g (0.01 mol) of N-(2-dimethylamino)-N-(2-pyridyl)-a-Boc-L-Lysinamide and 70mL of DMF. To this solution is added 2.19 g of methyl acetimidate hydrochloride. Triethylamine (TEA) (3.04 g, 0.03 mol) was added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The Boc-protected product, is then eluted with 10% aqueous pyridine.

After concentrating, the product produced in **Ex-2c** is deprotected by allowing it to stand in 2N HCl at 25°C for two hours. Concentrating in vacuo afforded L-N-(2-dimethylamino)-N-(2-pyridyl)- e-N-(iminoethyl)lysinamide tetrahydrochloride.



EXAMPLE 3

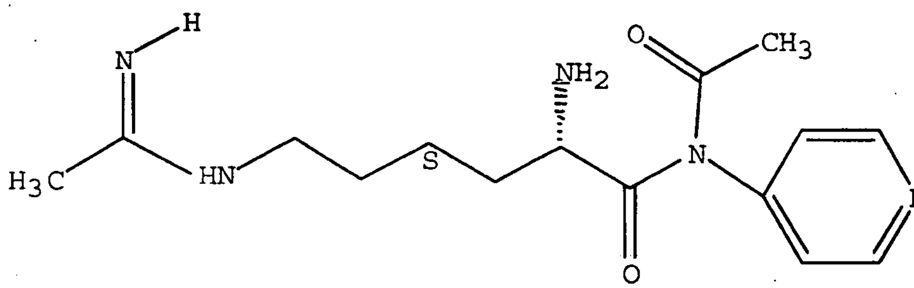
Ex-3a) To a stirring DMF solution of a-Z-S-(N-Boc-2-aminoethyl)- L-Cysteine (3.98 g, 10.0 mmol), N-(2-hydroxyethyl)-N-(2-thiazolyl)amine (1.39 g, 10.5 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-(2-hydroxyethyl)-N-(2-thiazolyl)-a-Z-S-(N-Boc-2-aminoethyl)-L-Cysteinamide.

Ex-3b) N-(2-hydroxyethyl)-N-(2-thiazolyl)-a-Z-S-(N-Boc-2-aminoethyl)-L-Cysteinamide is then dissolved in trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give N-(2-hydroxyethyl)-N-(2-thiazolyl)-a-Z- S-(2-aminoethyl)-L-Cysteinamide trifluoroacetate.

Ex-3c) To a 125 mL flask is added (10 mmol) of N-(2-hydroxyethyl)-N-(2-thiazolyl)-a-Z- S-(2-aminoethyl)-L-Cysteinamide and 70mL of water. This solution is adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 2.34 g of chloroacetaldoxime which is prepared immediately prior to use by the reaction of 3.55 g (0.06 mol) of acetaldoxime with 10.4 g (0.078 mol) of N-chlorosuccinimide in 65 mL of N,N-dimethylformamide at 0°C. The chloroacetaldoxime is isolated after three hours by extracting into diethyl ether and washing with aqueous NaCl. Drying with $MgSO_4$, filtration and concentration under 30°C affords the chloroacetaldoxime as a pale yellow oil. During the chloroacetaldoxime addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution was allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The Z-protected product is then eluted with 10% aqueous pyridine and lyophilized to remove solvent.

Ex-3d) N-(2-hydroxyethyl)-N-(2-thiazolyl)-a-Z- S-(2-(N-oximinoethyl)amino)ethyl)-L-Cysteinamide is dissolved in 25 ml of acetic anhydride containing a 0.1 g pyridine. After standing at room temperature for 2 hours, the reaction mixture is concentrated in vacuo to give N-(2-acetoxyethyl)-N-(2-thiazolyl)-a-Z-S-(2-(N-(2-acetoxyiminoethyl)amino)ethyl)-L-Cysteinamide.

N-(2-acetoxyethyl)-N-(2-thiazolyl)-a-Z-S-(2-(N-(2-acetoxyiminoethyl)amino)ethyl)-L-Cysteinamide is dissolved in 30% HBr in acetic acid to remove the Z-function generating the amino product N-(2-acetoxyethyl)-N-(2-thiazolyl)-S-(2-(N-(2-acetoxyiminoethyl)amino)ethyl)-L-Cysteinamide.



(7d)

EXAMPLE 4

Ex-4a) To a stirring DMF solution of a-Z-S-(N-Boc-2-aminoethyl)-L-Cysteine (3.98 g, 10.0 mmol), 4-aminopyridine (1.00 g, 10.5 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-(4-pyridyl)- a-Z-S-(N-Boc-2-aminoethyl)-L-Cysteinamide.

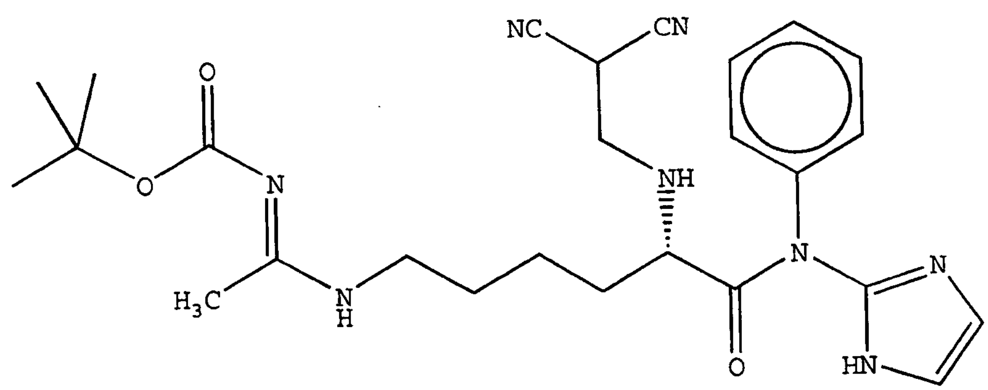
Ex-4b) N-(4-pyridyl)- a-Z-S-(N-Boc-2-aminoethyl)-L-Cysteinamide is then dissolved in trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give N-(4-pyridyl)- a-Z-S-(2-aminoethyl)-L-Cysteinamide trifluoroacetate.

Ex-4c) To a 125 mL flask is added (10 mmol) of N-(4-pyridyl)- a-Z-S-(2-aminoethyl)-L-Cysteinamide and 70mL of DMF. To this solution is added 4.14 g of

methyl N-Z-acetimidate. Triethylamine (TEA) (3.04 g, 0.03 mol) is added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The Z-protected product is then eluted with 10% aqueous pyridine.

Ex-4d) N-(4-pyridyl)-a-Z-S-(2-(N-(N-Z-iminoethyl)amino)ethyl)-L-Cysteinamide (0.005 mol) is thoroughly dried and dissolved in 25 ml of anhydrous THF. To the THF solution cooled to -78 °C, is added 1.1 equivalents of diisopropylamine followed by 1 equivalent on n-butyl lithium in hexane. Subsequently, 1.1 equivalents of acetyl chloride is added. After warming to room temperature, the reaction mixture is filterd to remove the precipitant and concentrated in vacuo to give N-acetyl-N-(4-pyridyl)-a-Z-S-(2-(N-(N-Z-iminoethyl)amino)ethyl)-L-Cysteinamide.

N-acetyl-N-(4-pyridyl)-a-Z-S-(2-(N-(N-Z-iminoethyl)amino)ethyl)-L-Cysteinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-functions generating the amino product N-acetyl-N-(4-pyridyl)-S-(2-(N-(iminoethyl)amino)ethyl)-L-Cysteinamide.



Example 5

Ex-5a) To a stirring DMF solution of a-Z-e-Boc-L-Lysine (3.80 g, 10.0 mmol), N-(phenyl)-2-aminoimidazole (1.67 g, 10.5 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-(phenyl)-N-(2-imidazolyl)-a-Z-e-Boc-L-Lysinamide.

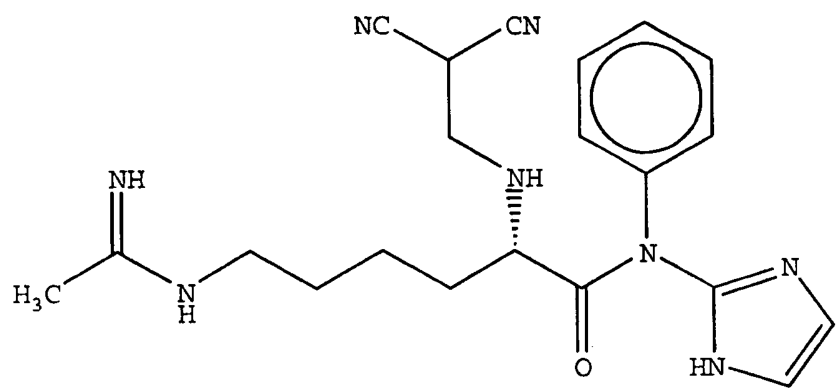
Ex-5b) N-(phenyl)-N-(2-imidazolyl)-a-Z-e-Boc-L-Lysinamide is then dissolved in trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give N-(phenyl)-N-(2-imidazolyl)-a-Z-L-Lysinamide trifluoroacetate.

To a 125 mL flask is added (10 mmol) of N-(phenyl)-N-(2-imidazolyl)-a-Z-L-Lysinamide and 70mL of DMF. To this solution is added 1.50g of methyl acetimidate hydrochloride. Triethylamine (TEA) (3.04 g, 0.03 mol) is added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The N-(phenyl)-N-(2-imidazolyl)-a-Z-e-(1-iminoethyl)-L-Lysinamide dihydrochloride is then eluted with 10% aqueous pyridine.

Ex-5c) A Boc protecting group is added to N-(phenyl)-N-(2-imidazolyl)-a-Z-e-(1-iminoethyl)-L-Lysinamide dihydrochloride using BOC-ON and the conditions in Fieser and Fieser (volume 6, page 91) to give N-(phenyl)-N-(2-imidazolyl)-a-Z-e-(N-Boc-1-iminoethyl)-L-lysinamide.

Ex-5d) N-(phenyl)-N-(2-imidazolyl)-a-Z-e-(N-Boc-1-iminoethyl)-L-Lysinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product N-(phenyl)-N-(2-imidazolyl)-e-(N-Boc-1-iminoethyl)-L-Lysinamide.

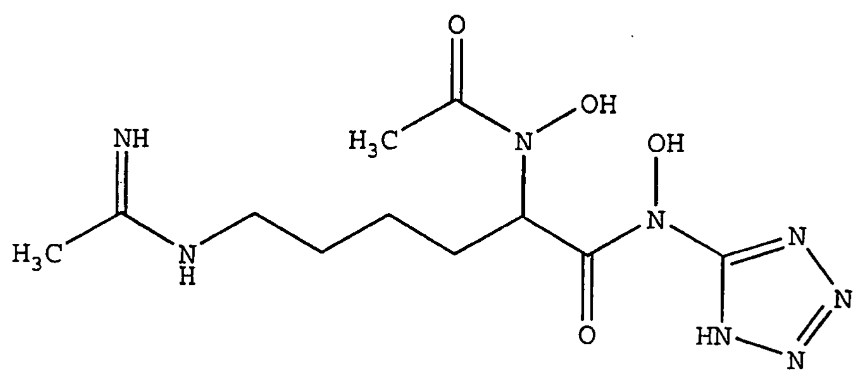
N-(phenyl)-N-(2-imidazolyl)-e-(N-Boc-1-iminoethyl)-L-Lysinamide is dissolved in ethanol. The solution is cooled in an ice bath. Triethylamine (TEA) (1 mL) is added, followed by 1,1-dicyanoethene. The reaction is allowed to warm to room temperature. Upon completion, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column giving, N-(phenyl)-N-(2-imidazolyl)-a-N-(2,2-dicyanoethyl)-e-(N-Boc-1-iminoethyl)-L-Lysinamide. This material is used in example 6.



Example 6

After concentrating, N-(phenyl)-N-(2-imidazolyl)-a-N-(2,2-dicyanoethyl)-e-(N-Boc-1-iminoethyl)-L-Lysinamide (prepared in example 5) is deprotected by allowing it to stand in dioxane and 2N HCl at 25°C for three hours. The reaction

mixture is then concentrated in vacuo to give N-(phenyl)-N-(2-imidazolyl)-a-N-(2,2-dicyanoethyl)-e-(1-iminoethyl)-L-lysinamide trihydrochloride.



Example 7

Ex-7a) e-Amino-a-hydroxyhexanoic acid (1.47 g, 10 mmol) is allowed to stir with t-butoxycarbonylazide (1.49 g, 10.5 mmol) and MgO (0.47 g, 10.5 mmol) in dioxane/water solution. Upon completion, the magnesium salts are removed by filtration. The e-(N-Boc-amino)-a-hydroxy hexanoic acid solution is cooled in an ice bath and treated with acetic anhydride (1.07 g, 10.5 mmol) and triethyl amine (TEA) (1.06 g, 10.5 mmol) and stirred. Upon completion the mixture is concentrated in vacuum. The resulting material is passed through a reverse phase chromatographic column, giving e-(N-Boc-amino)-a-(acetoxy)hexanoic acid.

Ex-7b) To a stirring DMF solution of e-(N-Boc-amino)-a-(acetoxy) hexanoic acid (2.68 g, 9 mmol), N-5-tetrazoyl hydroxylamine hydrochloride (1.39 g, 9.5 mmol), and 1-hydroxybenzotriazole hydrate (1.31 g, 9.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.74 g, 9.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in

vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-hydroxy-N-(5-tetrazoyl)-e-(N-Boc-amino)-a-(acetoxy) hexanamide.

Ex-7c) N-Hydroxy-N-(5-tetrazoyl)-e-(N-Boc-amino)-a-(acetoxy) hexanamide (2.7 g, 8 mmol) is dissolved in ethanol and treated with sodium hydroxide (0.3 g, 8 mmol). When the acetyl group is removed the mixture is concentrated in vacuum and passed through a reverse phase chromatographic column, giving N-hydroxy-N-(5-tetrazoyl)-e-(N-Boc-amino)-a-hydroxyhexanamide.

Ex-7d) N-Hydroxy-N-(5-tetrazoyl)-e-(N-Boc-amino)-a-hydroxy hexanamide (2.2 g, 8 mmol) is dissolved in DMSO and treated with 1,3-dicyclohexylcarbodimide (DCC) (1.6 g, 8 mmol) and phosphoric acid. The reaction is stirred at room temperature. Upon completion, methylene chloride is added to the mixture and it is washed with 10% aqueous sodium bicarbonate, water and brine. The methylene chloride layer is dried over $MgSO_4$, filtered and solvents removed in vacuo. The product is passed through a reverse phase chromatographic column, giving N-hydroxy-N-(5-tetrazoyl)-e-(N-Boc-amino)-2-oxohexanamide.

Ex-7e) N-Hydroxy-N-(5-tetrazoyl)-e-(N-Boc-amino)-2-oxohexanamide (2.1 g, 8 mmol) is dissolved in ethanol and treated with hydroxylamine hydrochloride (0.6 g, 8 mmol) and sodium carbonate (1 g). The reaction mixture is filtered and concentrated in vacuum, giving crude N-hydroxy-N-(5-tetrazoyl)-e-(N-Boc-amino)-2-oximinohexanamide.

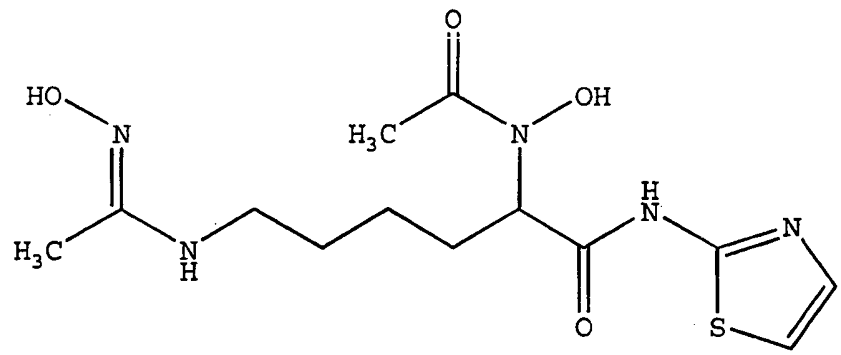
Ex-7f) N-Hydroxy-N-(5-tetrazoyl)-e-(N-Boc-amino)-2-oximino hexanamide (prepared in example 7) is cooled in an ice bath and 1.0M borane-tetrahydrofuran complex (8.5 mL) added dropwise. When addition is complete, the reaction is allowed to warm to room temperature. Upon complete reduction 1 mL of water is added. The reaction is concentrated at reduced pressure. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50

Cation exchange column. The column is washed with water. N-hydroxy-N-(5-tetrazoyl)-e-(N-Boc-amino)-2-oxaminohexanamide is then eluted with 10% aqueous pyridine.

Ex-7g) After concentrating, the product is treated with one equivalent of acetic anhydride (0.82 g, 8 mmol) and triethyl amine (TEA) (0.80 g, 8 mmol) and stirred. Upon completion the mixture is concentrated in vacuum. The resulting material is passed through a reverse phase chromatographic column, giving N-hydroxy-N-(5-tetrazoyl)-e-(N-Boc-amino)-a-(N-hydroxy-N-acetamido)hexanamide.

Ex-7h) N-hydroxy-N-(5-tetrazoyl)-e-(N-Boc-amino)- a-(N-hydroxy-N-acetamido) hexanamide is deprotected by allowing it to stand in dioxane and 2N HCl at 25°C for two hours. Concentrating in vacuo afforded N-hydroxy-N-(5-tetrazoyl)-e-amino- a-(N-hydroxy-N-acetamido)hexanamide hydrochloride.

To a 125 mL flask is added 1.98 g (7 mmol) N-hydroxy-N-(5-tetrazoyl)-e-amino- a-(N-hydroxy-N-acetamido)hexanamide hydrochloride and 50 mL of DMF. To this solution is added 1.05 g of methyl acetimidate hydrochloride. Triethylamine (TEA) (2.03 g, 20 mmol) is added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The N-hydroxy-N-(5-tetrazoyl)-e-(N-(1-iminoethyl))amino- a-(N-hydroxy-N-acetamido)hexanamide is then eluted with 10% aqueous pyridine and solvents removed and compound dried.



Example 8

e-(N-Boc-amino)-a-(acetoxy)hexanoic acid is prepared as in example 7.

Ex-8a) To a stirring DMF solution of e-(N-Boc-amino)-a-(acetoxy) hexanoic acid (2.97 g, 10 mmol), 2-aminothiazole (1.05 g, 10.5 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-(2-thiazolyl)-e-(N-Boc-amino)-a-(acetoxy)hexanamide.

Ex-8b) N-(2-Thiazolyl)-e-(N-Boc-amino)-a-(acetoxy)hexanamide (3.5 g, 10 mmol) is dissolved in ethanol and treated with sodium hydroxide (4.0 g, 10 mmol). When the acetyl group is removed, the mixture is concentrated in vacuum and passed through a reverse phase chromatographic column, giving N-(2-thiazolyl)-e-(N-Boc-amino)-a-(hydroxy)hexanamide.

Ex-8c) N-(2-Thiazolyl)-e-(N-Boc-amino)-a-(hydroxy)hexanamide (3.0 g, 9 mmol) is dissolved in DMSO and treated with 1,3-dicyclohexylcarbodimide (DCC) (1.8 g,

9 mmol) and phosphoric acid. The reaction is stirred at room temperature. Upon completion, methylene chloride is added to the mixture, and it is washed with 10% aqueous sodium bicarbonate, water and brine. The methylene chloride layer is dried over $MgSO_4$, filtered and solvents removed in vacuo. The product is passed through a reverse phase chromatographic column, giving N-(2-thiazolyl)-e-(N-Boc-amino)-2-oxohexanamide.

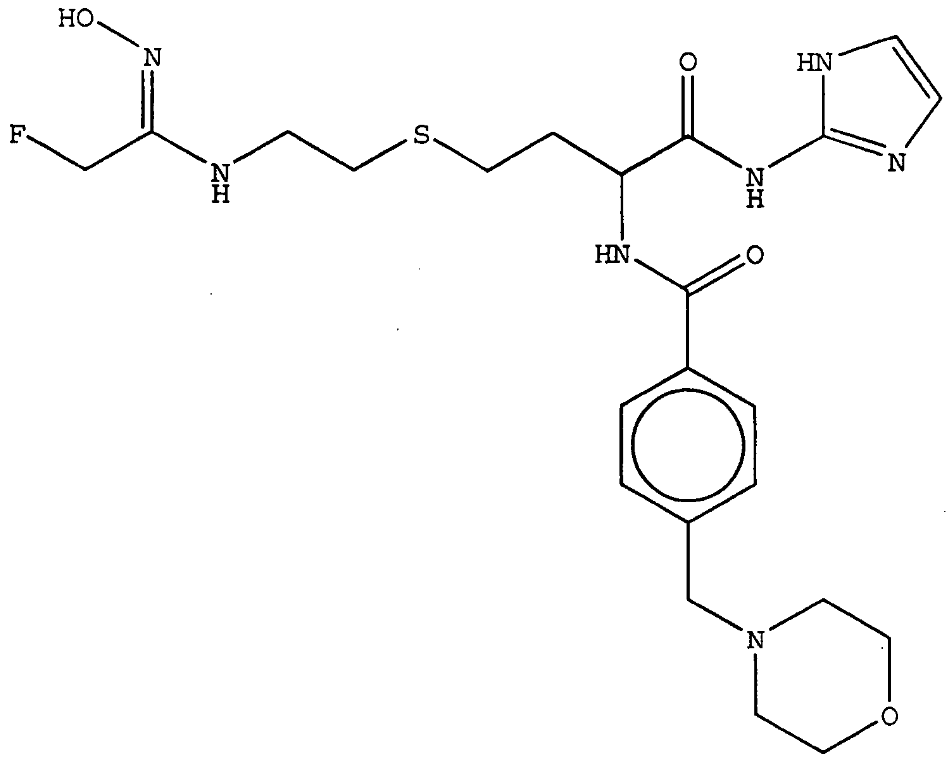
Ex-8d) N-(2-Thiazolyl)-e-(N-Boc-amino)-2-oxohexanamide (2.8 g, 9 mmol) is dissolved in ethanol and treated with hydroxylamine hydrochloride (0.65 g, 9 mmol) and sodium carbonate (1 g). Upon completion, the reaction mixture is filtered and concentrated in vacuum, giving crude N-(2-thiazolyl)-e-(N-Boc-amino)-2-oximinohexanamide.

Ex-8e) N-(2-Thiazolyl)-e-(N-Boc-amino)-2-oximinohexanamide (prepared in example 9) is cooled in an ice bath and 1.0M borane-tetrahydrofuran complex (9.5 mL) added dropwise. When addition is complete, the reaction is allowed to warm to room temperature. Upon complete reduction 1 mL of water is added. The reaction is concentrated in vacuum. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. N-(2-thiazolyl)-e-(N-Boc-amino)-2-oxamidohexanamide is then eluted with 10% aqueous pyridine.

Ex-8f) After concentrating, the product is cooled in an ice bath, treated with one equivalent of acetic anhydride (0.92 g, 9 mmol) and triethyl amine (TEA) (0.90 g, 9 mmol), stirred, and allowed to warm to room temperature. Upon completion the mixture is concentrated in vacuum. The resulting material is passed through a reverse phase chromatographic column, giving N-(2-thiazolyl)-e-(N-Boc-amino)-a-(N-hydroxy-N-acetamido)hexanamide.

Ex-8g) N-(2-Thiazolyl)-e-(N-Boc-amino)-a-(N-hydroxy-N-acetamido) hexanamide is deprotected by allowing it to stand in dioxane and 2N HCl at 25°C for two hours. Concentrating in vacuo afforded N-(2-thiazolyl)-e-(amino)-a-(N-hydroxy-N-acetamido)hexanamide hydrochloride.

To a 125 mL flask is added 2.89 g (8 mmol) of afforded N-(2-thiazolyl)-e-(amino)-a-(N-hydroxy-N-acetamido)hexanamide hydrochloride and 70mL of water. This solution is adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 1.49 g of chloroacetaldoxime which is prepared immediately prior to use by the reaction of 5.38 g (0.05 mol) of acetaldoxime with 8 g (0.060 mol) of N-chlorosuccinimide in 65 mL of N,N-dimethylformamide at 0°C. The chloroacetaldoxime is isolated after three hours by extracting into diethyl ether and washing with aqueous NaCl. Drying with $MgSO_4$, filtration and concentration under 30°C afforded the chloroacetaldoxime as a pale yellow oil. During the chloroacetaldoxime addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The product N-(2-thiazolyl)-e-(N-(1-oximinoethyl)amino)-a-(N-hydroxy-N-acetamido)hexanamide is then eluted with 10% aqueous pyridine. The solvents are removed, and the compound dried.



Example 9

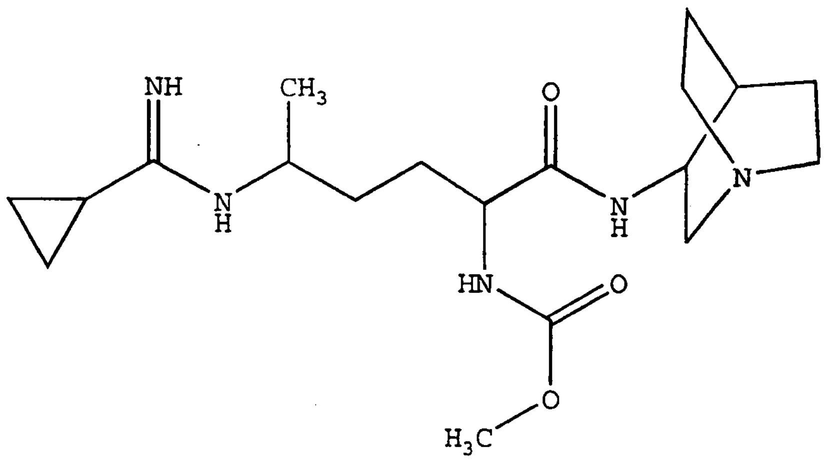
Ex-9a) a-(N-Boc)-S-(N-Z-2-aminoethyl)-D,L-Homocysteine (4.38 g, 11 mmol) is coupled with 2-aminoimidazole (0.95 g, 11.5 mmol) following the procedure used in **Ex-1a**. The result is N-(2-imidazolyl)- a-(N-Boc)-S-(N-Z-2-aminoethyl)-D,L-Homocysteinamide.

Ex-9b) N-(2-Imidazolyl)- a-(N-Boc)-S-(N-Z-2-aminoethyl)-D,L-homocysteinamide is then dissolved in trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give N-(2-imidazolyl)-S-(N-Z-2-aminoethyl)-D,L-Homocysteinamide trifluoroacetate.

Ex-9c) N-(2-Imidazolyl)-S-(N-Z-2-aminoethyl)-D,L-homocysteinamide (10 mmol) is cooled in an ice bath and treated with 4-morpholinomethylbenzoyl chloride (2.50 g, 10.5 mmol) and triethyl amine (TEA) (2.1 g, 21 mmol) and stirred. The mixture is allowed to warm to room temperature. Upon completion the mixture is concentrated in vacuum. The resulting material is passed through a reverse phase chromatographic column, giving N-(2-imidazolyl)-S-(N-Z-2-aminoethyl)-a-N-(4-morpholinomethylbenzoyl)-D,L-homocysteinamide.

Ex-9d) N-(2-imidazolyl)-S-(N-Z-2-aminoethyl)-a-N-(4-morpholinomethylbenzoyl)-D,L-homocysteinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product N-(2-imidazolyl)-S-(2-aminoethyl)- a-N-(4-morpholinomethylbenzoyl)-D,L-homocysteinamide.

To a 125 mL flask is added 4.29 g (10 mmol) of afforded N-(2-imidazolyl)-S-(2-aminoethyl)- a-N-(4-morpholinomethylbenzoyl)-D,L-homocysteinamide and 70mL of water. This solution is adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 2.23 g of 1-chloro-2-fluoroacetaldoxime which is prepared immediately prior to use by the reaction of 5.38 g (0.05 mol) of 2-fluoroacetaldoxime with 8 g (0.060 mol) of N-chlorosuccinimide in 65 mL of N,N-dimethylformamide at 0°C. The 1-chloro-2-fluoroacetaldoxime is isolated after three hours by extracting into diethyl ether and washing with aqueous NaCl. Drying with $MgSO_4$, filtration and concentration under 30°C affords 1-chloro-2-fluoro acetaldoxime as a pale yellow oil. During 1-chloro-2-fluoroacetaldoxime addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The product N-(2-imidazolyl)- S-(2-(N-(2-fluoro-1-oximinoethyl)amino)ethyl)- a-N-(4-morpholinomethylbenzoyl)-D,L-homocysteinamide is then eluted with 10% aqueous pyridine. The solvents are removed, and the compound dried.



Example 10

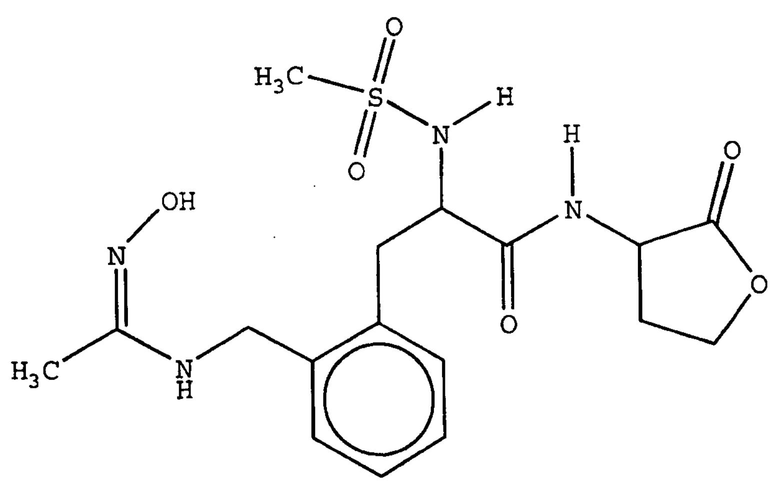
Ex-10a) d-Z-a-(N-Boc)-D,L-5-Methylornithine (4.03 g, 11 mmol) is coupled with 3-aminoquiniclidine (1.45 g, 11.5 mmol) following the procedure used in **Ex-1a**. The result is N-(3-quiniclidinyl)- d-Z-a-(N Boc)-D,L- methylornithinamide.

Ex-10b) N-(3-Quiniclidinyl)- d-Z-a-(N-Boc)-D,L-Methylornithinamide is then dissolved in trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give N-(3-quiniclidinyl)- d-Z-D,L- methylornithinamide trifluoroacetate.

Ex-10c) The product N-(3-quiniclidinyl)- d-Z-D,L- Methylornithinamide (10 mmol) is cooled in an ice bath and treated with methylchloroformate (0.97 g, 10.5 mmol) and triethyl amine (TEA) (2.1 g, 21 mmol). The mixture is allowed to warm to room temperature. Upon completion the mixture is concentrated in vacuum. The resulting material is passed through a reverse phase chromatographic column, giving N-(3-quiniclidinyl)- d-Z-a-(N-methoxyformyl)-D,L-methylornithinamide.

Ex-10d) N-(3-Quiniclidinyl)- d-Z-a-(N-methoxyformyl)-D,L- methylornithinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product N-(3-quiniclidinyl)-a-(N-methoxyformyl)-D,L-methylornithinamide.

To a 125 mL flask is added 2.88 g (9 mmol) N-(3-quiniclidinyl)-a-(N-methoxyformyl)-D,L- Methylornithinamide) and 50 mL of DMF. To this solution is added 2.57 g of methyl cyclopropylformimidate hydrochloride. Triethylamine (TEA) (1.82 g, 18 mmol) is added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. N-(3-quiniclidinyl)- d-N-(1-imino-1-cyclopropylmethyl)-a-(N-methoxyformyl)-D,L-methylornithinamide is then eluted with 10% aqueous pyridine and solvents removed and compound dried.



Example 11

Ex-11a) a-(N-Boc)-*ortho*-(N-Z-aminomethyl)phenylalanine (4.54 g, 11 mmol) is coupled with a-amino-g-butyrolactone hydrobromide (2.07 g, 11.5 mmol) following the procedure used in **Ex-1a**. The result is N-(2-g-butyrolactone)- a-(N-Boc)-*ortho*-(N-Z-aminomethyl) phenylalaninamide.

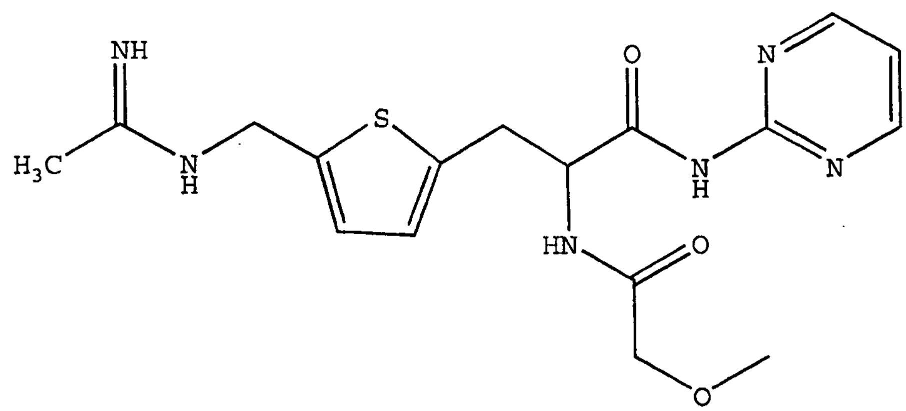
Ex-11b) N-(2-g-Butyrolactone)- a-(N-Boc)-*ortho*-(N-Z-aminomethyl) phenylalaninamide is then dissolved in trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give N-(2-g-butyrolactone)-*ortho*-(N-Z-aminomethyl)phenylalaninamide trifluoroacetate.

Ex-11c) N-(2-g-Butyrolactone)-*ortho*-(N-Z-aminomethyl)phenyl alaninamide (10 mmol) is cooled to -78°C and treated with methanesulfonyl chloride (1.20 g, 10.5 mmol) and triethyl amine (TEA) (2.1 g, 21 mmol). The mixture is allowed to warm to room temperature. Upon completion the mixture is concentrated in vacuum. The resulting material is passed through a reverse phase chromatographic column, giving N-(2-g-butyrolactone)-a-(N-methansulfonyl)-*ortho*-(N-Z-aminomethyl)phenylalaninamide.

Ex-11d) N-(2-g-Butyrolactone)-a-(N-methansulfonyl)-*ortho*-(N-Z-aminomethyl)phenylalaninamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product N-(2-g-butyrolactone)-a-(N-methansulfonyl)-*ortho*-(aminomethyl)phenylalaninamide.

To a 125 mL flask is added 3.54 g (10 mmol) of afforded N-(2-g-butyrolactone)-a-(N-methansulfonyl)-*ortho*-(aminomethyl) phenylalaninamide and 70mL of water.

This solution is adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 2.34 g of chloroacetaldoxime which is prepared immediately prior to use by the reaction of 3.55 g (0.06 mol) of acetaldoxime with 10.4 g (0.078 mol) of N-chlorosuccinimide in 65 mL of N,N-dimethylformamide at 0°C. The chloroacetaldoxime is isolated after three hours by extracting into diethyl ether and washing with aqueous NaCl. Drying with $MgSO_4$, filtration and concentration under 30°C affords chloroacetaldoxime as a pale yellow oil. During chloroacetaldoxime addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The product N-(2-g-butyrolactone)-a-(N-methansulfonyl)-*ortho*-(N-(1-oximinoethyl))aminomethyl)phenylalaninamide is then eluted with 10% aqueous pyridine. The solvents are removed, and the compound dried.



Example 12

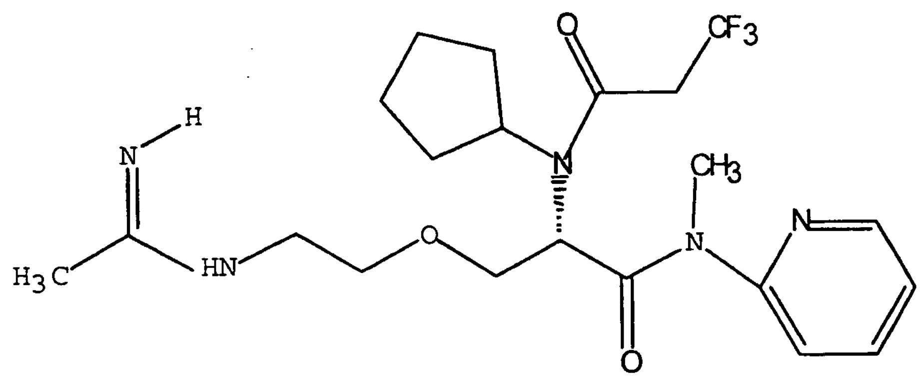
Ex-12a) 3-(5-(N-Z-Aminomethyl)thiophenyl)-2-(N-Boc-amino)propionic acid (4.62 g, 11 mmol) is coupled with 2-aminopyrimidine (1.09 g, 11.5 mmol) following the procedure used in **Ex-1a**. The result is N-(2-pyrimidinyl)- 3-(5-(N-Z-Aminomethyl)thiophenyl)-2-(N-Boc-amino) propionamide.

Ex-12b) N-(2-pyrimidinyl)- 3-(5-(N-Z-Aminomethyl)thiophenyl)-2-(N-Boc-amino)propionamide is then dissolved in trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give N-(2-pyrimidinyl)- 3-(5-(N-Z-Aminomethyl)thiophenyl)-2-aminopropionamide trifluoroacetate.

Ex-12c) The product N-(2-pyrimidinyl)- 3-(5-(N-Z-Aminomethyl)thiophenyl)-2-aminopropionamide trifluoroacetate is cooled in an ice bath and treated with methyoxyacetyl chloride (1.14 g, 10.5 mmol) and triethyl amine (TEA) (2.1 g, 21 mmol). The mixture is allowed to warm to room temperature. Upon completion the mixture is concentrated in vacuum. The resulting material is passed through a reverse phase chromatographic column, giving The product N-(2-pyrimidinyl)- 3-(5-(N-Z-Aminomethyl)thiophenyl)-2-acetamidopropionamide.

Ex-12d) N-(2-pyrimidinyl)- 3-(5-(N-Z-Aminomethyl)thiophenyl)-2-acetamidopropionamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product N-(2-pyrimidinyl)- 3-(5-(aminomethyl)thiophenyl)-2-acetamidopropionamide.

To a 125 mL flask is added 2.88 g (9 mmol) N-(2-pyrimidinyl)- 3-(5-(aminomethyl)thiophenyl)-2-acetamidopropionamide and 50 mL of DMF. To this solution is added 1.97 g of methyl acetimidate hydrochloride. Triethylamine (TEA) (2.74 g, 27 mmol) is added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The product N-(2-pyrimidinyl)- 3-(5-(N-(1-iminoethyl)amino)methyl)thiophenyl)-2-acetamidopropionamide is then eluted with 10% aqueous pyridine and solvents removed and compound dried.



EXAMPLE 13

Ex-13a) To a stirring DMF solution of α-Boc-O-(2-(N-Z-amino)ethyl)-L-serine (3.82 g, 10.0 mmol), 2-methylaminopyridine (1.14 g, 10.5 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-methyl-N-(2-pyridyl)-α-Boc-O-(2-(N-Z-amino)ethyl)-L-serinamidev.

Ex-13b) N-methyl-N-(2-pyridyl)-α-Boc-O-(2-(N-Z-amino)ethyl)-L-serinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product N-methyl-N-(2-pyridyl)-α-Boc-O-(2-aminoethyl)-L-serinamide.

Ex-13c) To a 125 mL flask was added 2.71 g (0.008 mol) of N-methyl-N-(2-pyridyl)-α-Boc-O-(2-aminoethyl)-L-serinamide and 70mL of DMF. To this solution was added 4.14 g of methyl N-Z-acetimidate. Triethylamine (TEA) (3.04 g, 0.03 mol) is added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The Boc-protected product is then eluted with 10% aqueous pyridine.

Ex-13d) N-methyl-N-(2-pyridyl)-α-Boc-O-(2-(N-(1-iminoethyl)amino)ethyl)-L-serinamide (1.9 g, 0.005 mol) is added to 50 ml of THF containing 1.01 grams of triethylamine. Carbobenzoxy chloride (Z-Cl; 1.03 g, 0.006 mol) is added and stirred at room temperature for 24 hours. The reaction mixture is concentrated in vacuo to remove THF and slurried with 50 ml. methylene chloride. The methylene chloride is washed with water, concentrated in vacuo at 50 °C, and residue purified by chromatography to afford N-methyl-N-(2-pyridyl)-α-Boc-O-(2-(N-(N-Z-1-iminoethyl)amino)ethyl)-L-serinamide.

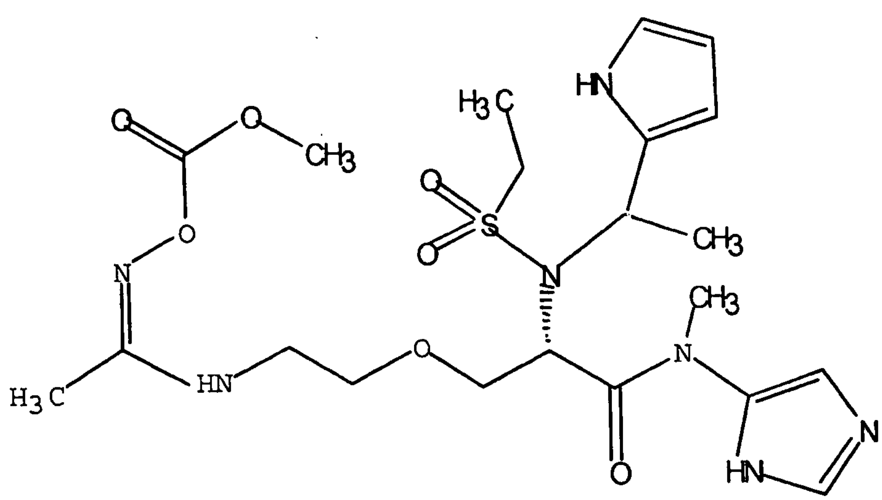
Ex-13e) N-methyl-N-(2-pyridyl)-α-Boc-O-(2-(N-(N-Z-1-iminoethyl)amino)ethyl)-L-serinamide is then dissolved in trifluoroacetic acid and allowed to stand at room temperature with spectroscopic monitoring until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give N-methyl-N-(2-pyridyl)-O-(2-(N-(N-Z-iminoethyl)amino)ethyl)-L-serinamide trifluoroacetate.

Ex-13f) N-methyl-N-(2-pyridyl)-O-(2-(N-(N-Z-iminoethyl)amino)ethyl)-L-serinamide trifluoroacetate is added to 50 ml of toluene in 100 ml. reaction flask. After adding 0.761 g of p-toluenesulfonic acid and 0.504 g (0.006 mol) cyclopentanone, the reaction mixture is refluxed with azeotropic distillation complete removal of water using a Dean-Stark trap. After cooling, the solvent and excess cyclopentanone is removed in vacuo to give an essentially quantitative yield

of the imine N-methyl-N-(2-pyridyl)-α-(N-cyclopentylene)-O-(2-(N-(N-Z-1-iminoethyl)amino)ethyl)-L-serinamide toluenesulfonate salt.

Ex-13g) N-methyl-N-(2-pyridyl)-α-(N-cyclopentylene)-O-(2-(N-(N-Z-1-iminoethyl)amino)ethyl)-L-serinamide is placed in a mixture with anhydrous toluene, a hydrogenation catalyst such as palladium on carbon, and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to reduce the imine and remove the Z-function generating the p-toluenesulfonate salt of the amino product N-methyl-N-(2-pyridyl)-α-(N-cyclopentyl)-O-(2-(N-(1-iminoethyl)amino)ethyl)-L-serinamide.

The p-toluenesulfonate salt of N-methyl-N-(2-pyridyl)-α-(N-cyclopentyl)-O-(2-(N-(1-iminoethyl)amino)ethyl)-L-serinamide (0.003 mol) is placed in 20 ml of anhydrous THF containing 1.01 grams of triethylamine. After cooling to -78 °C, 3,3,3-trifluoropropanoic anhydride (0.762g, 0.0032 mol) in 10 ml anhydrous THF is added over 20 minutes. After warming to room temperature, the solvent is removed in vacuo, 50 ml methylene chloride added along with 20 ml of water. The methylene chloride layer is separated, back washed with water, and concentrated to afford N-methyl-N-(2-pyridyl)-α-(N-cyclopentyl)-α-N-(3,3,3-trifluoropropanoyl)-O-(2-(N-(1-iminoethyl)amino)ethyl)-L-serinamide which can be purified if needed chromatographically.



EXAMPLE 14

Ex-14a) To a stirring DMF solution of α-Z-O-(2-(N-Boc-amino)ethyl)-L-serine (3.82 g, 10.0 mmol), 4-methylaminoimidazole (1.01 g, 10.5 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-methyl-N-(4-imidazolyl)-α-Z-O-(2-(N-Boc-amino)ethyl)-L-serinamide.

Ex-14b) N-methyl-N-(4-imidazolyl)-α-Z-O-(2-(N-Boc-amino)ethyl)-L-serinamide is dissolved in trifluoroacetic acid and allowed to stand at room temperature with spectroscopic monitoring until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give the amino product N-methyl-N-(4-imidazolyl)-α-Z-O-(2-aminoethyl)-L-serinamide trifluoroacetate.

Ex-14c) N-methyl-N-(4-imidazolyl)-α-Z-O-(2-aminoethyl)-L-serinamide is converted to N-methyl-N-(4-imidazolyl)-α-Z-O-(2-(N-(1-oximinoethyl))amino)ethyl)-L-serinamide as described for the conversion of Page 97 to Page 98.

Ex-14d) N-methyl-N-(4-imidazolyl)-α-Z-O-(2-(N-(1-oximinoethyl)amino)ethyl)-L-serinamide (2.05 g, 0.005 mol) is added to 50 ml of THF containing 1.01 grams of triethylamine. Methyl chloroformate (0.567 g, 0.006 mol) is added and stirred at room temperature for 24 hours. The reaction mixture is concentrated in vacuo to remove THF and slurried with 50 ml. methylene chloride. The methylene chloride is washed with water, concentrated in vacuo at 50 °C, and residue purified by

chromatography to afford N-methyl-N-(4-imidazolyl)-α-Z-O-(2-(N-(1-(O-(methoxycarbonyl)oximino)ethyl)amino)ethyl)-L-serinamide.

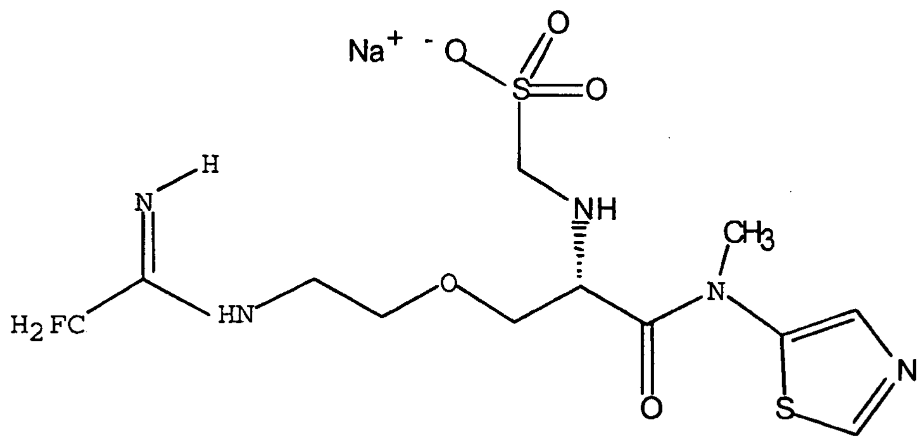
Ex-14e) N-methyl-N-(4-imidazolyl)-α-Z-O-(2-(N-(1-(O-(methoxycarbonyl)oximino)ethyl)amino)ethyl)-L-serinamide is then dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to give N-methyl-N-(4-imidazolyl)-O-(2-(N-(1-(O-(methoxycarbonyl)oximino)ethyl)amino)ethyl)-L-serinamide.

Ex-14f) N-methyl-N-(4-imidazolyl)-O-(2-(N-(1-(O-(methoxycarbonyl) oximino)ethyl)amino)ethyl)-L-serinamide (1.34 g, 0.004 mol) is added to 50 ml of toluene in 100 ml. reaction flask. After adding 0.761 g of p-toluenesulfonic acid and 0.546 g (0.005 mol) 2-acetylpyrrole, the reaction mixture is refluxed with azeotropic distillation complete removal of water using a Dean-Stark trap. After cooling, the solvent is removed in vacuo to give an essentially quantitative yield of the imine N-methyl-N-(4-imidazolyl)-α-(N-(1-pyrrolylethylenyl))-O-(2-(N-(1-(O-(methoxycarbonyl) oximino)ethyl)amino)ethyl)-L-serinamide toluenesulfonate salt.

Ex-14g) N-methyl-N-(4-imidazolyl)-α-(N-(1-pyrrolylethylenyl))-O-(2-(N-(1-(O-(methoxycarbonyl)oximino)ethyl)amino)ethyl)-L-serinamide toluenesulfonate salt is placed in a mixture with anhydrous toluene, a hydrogenation catalyst such as palladium on carbon, and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to reduce the imine generating the p-toluenesulfonate salt of the amino product N-methyl-N-(4-imidazolyl)-α-(N-(1-pyrrolylethylenyl))-O-(2-(N-(1-(O-(methoxycarbonyl)oximino)ethyl)amino)ethyl)-L-serinamide.

The p-toluenesulfonate salt N-methyl-N-(4-imidazolyl)-α-(N-(1-pyrrolylethylenyl))-O-(2-(N-(1-(O-(methoxycarbonyl) oximino)ethyl)amino)ethyl)-L-serinamide (0.003 mol) is placed in 20 ml of anhydrous THF containing 1.01

grams of triethylamine. After cooling to -78 °C, ethanesulfonyl chloride (0.412 g, 0.0032 mol) in 10 ml anhydrous THF is added over 20 minutes. After warming to room temperature, the solvent is removed in vacuo, 50 ml methylene chloride added along with 20 ml of water. The methylene chloride layer is separated, back washed with water, and concentrated to afford N-methyl-N-(4-imidazolyl)-α-(N-(1-pyrrolylethylenyl))-O-(2-(N-(1-(O-(methoxycarbonyl) oximino)ethyl)amino)ethyl)-α-(N-ethanesulfonyl)-L-serinamide which can be purified if needed chromatographically.



EXAMPLE 15

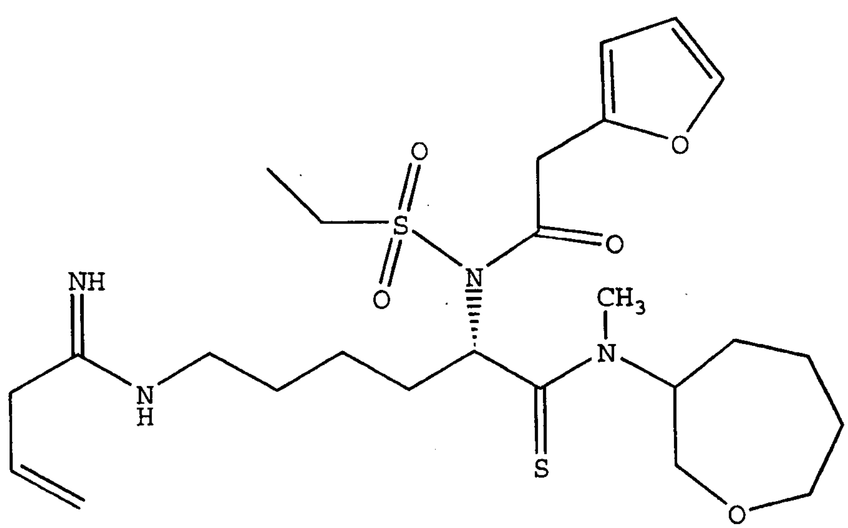
Ex-15a) α-Z-O-(2-(N-Boc-amino)ethyl)-L-serine (3.82 g, 10.0 mmol) is reacted with 4-methylaminothiazole (1.20 g, 10.5 mmol) as described in Example 16 to yield N-methyl-N-(4-thiazolyl)-α-Z-O-(2-(N-Boc-amino)ethyl)-L-serinamide.

Ex-15b) N-(4-thiazolyl)-α-Z-O-(2-(N-Boc-amino)ethyl)-L-serinamide is converted to N-methyl-N-(4-thiazolyl)-α-Z-O-(2-aminoethyl)-L-serinamide as described in Example 16.

Ex-15c) N-methyl-N-(4-thiazolyl)-α-Z-O-(2-aminoethyl)-L-serinamide is converted to N-methyl-N-(4-thiazolyl)-α-Z-O-(2-(N-(2-fluoro-1-iminoethyl)amino)ethyl)-L-serinamide using methyl 2-fluoroacetimidate hydrochloride as described in **Ex-2c**.

Ex-15d) N-methyl-N-(4-thiazolyl)-α-Z-O-(2-(N-(2-fluoro-1-iminoethyl)amino)ethyl)-L-serinamide is then dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to give N-methyl-N-(4-thiazolyl)-O-(2-(N-(2-fluoro-1-iminoethyl)amino)ethyl)-L-serinamide.

N-methyl-N-(4-thiazolyl)-O-(2-(N-(2-fluoro-1-iminoethyl)amino)ethyl)-L-serinamide (1.19 g, 0.004 mol) is reacted with sodium hydroxymethylsulfonate in aqueous solution at a pH of 10 using a procedure described by L. Maier (Phosphorus, Sulfur, Silicon Related Elements (1990), vol. 47, pages 43-46) to form sodium α-N-(N-methyl-N-(4-thiazolyl)-O-(2-(N-(2-fluoro-1-iminoethyl)amino)ethyl)-L-serinamido)methanesulfonate.



Example 16

Ex-16a) e-Z-a-Boc-L-Lysine (4.39 g, 12 mmol) is reacted with 3(N-methylamino)oxacycloheptane (1,61 g, 12.5 mmol) as described in **Ex-2a** to yield N-methyl-N-(3-oxacycloheptyl)-e-Z-a-Boc-L-Lysinamide.

Ex-16b) N-Methyl-N-(3-oxacycloheptyl)-e-Z-a-Boc-L-Lysinamide is then subjected to conditions to remove the Z protecting group as described in **Ex-2b** to give N-methyl-N-(3-oxacycloheptyl)-a-Boc-L-Lysinamide.

Ex-16c) The resulting N-methyl-N-(3-oxacycloheptyl)-a-Boc-L-Lysinamide (3.77 g, 11 mmol) is reacted with methyl but-3-eneimidate hydrochloride (2.90 g) as described in **Ex-2c** in Example 2 to yield N-methyl-N-(3-oxacycloheptyl)- a-Boc -e-N-(1-imino-3-butenyl)-L-Lysinamide.

Ex-16d) N-Methyl-N-(3-oxacycloheptyl)- a-Boc -e-N-(1-imino-3-butenyl)-L-Lysinamide is then subjected to conditions to remove the Boc protecting group as described in **Ex-2d** to give N-methyl-N-(3-oxacycloheptyl)-e-N-(1-imino-3-butenyl)-L-Lysinamide.

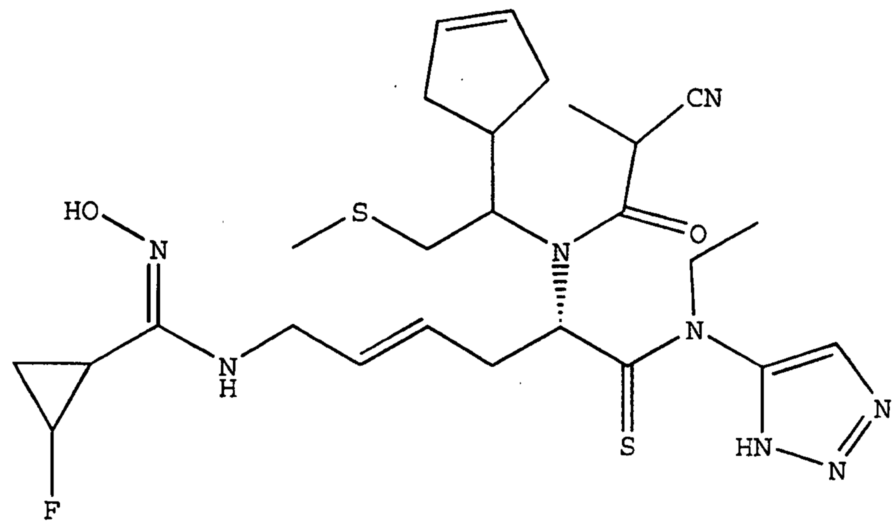
Ex-16e) N-Methyl-N-(3-oxacycloheptyl)-e-N-(1-imino-3-butenyl)-L-Lysinamide (3.41 g, 11 mmol) is treated with one equivalent 2,2,2-trichloroethyl chloroformate (2.22 g, 11 mmol) and sodium carbonate in aqueous tetrahydrofuran under the conditions described by D. Gravel in Canadian Journal of Chemistry, 50, 3846, 1972 to give N-methyl-N-(3-oxacycloheptyl)-a-N-(2,2,2-trichloroethoxyformyl)-e-N-(1-imino-3-butenyl)-L-Lysinamide.

Ex-16f) N-Methyl-N-(3-oxacycloheptyl)-a-N-(2,2,2-trichloroethoxyformyl)-e-N-(1-imino-3-butenyl)-L-Lysinamide (5.10 g, 10 mmol) is treated with Lawesson's

Reagent under the conditions described in Chem. Reviews, 84, 17-30, 1984 and references cited therein. To yield N-methyl-N-(3-oxacycloheptyl)-a-N-(2,2,2-trichloroethoxythioformyl)-e-N-(1-imino-3-butenyl)-L-thionolysinamide.

Ex-16g) N-Methyl-N-(3-oxacycloheptyl)-a-N-(2,2,2-trichloroethoxythioformyl)-e-N-(1-imino-3-butenyl)-L-thionolysinamide (4.89g, 10 mmol) is dissolved in acetic acid and treated with zinc dust (0.65g, 10 mmol). After stirring two hours, saturated aqueous sodium carbonate is added. The solids are removed by filtration. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The product N-methyl-N-(3-oxacycloheptyl)-e-N-(1-imino-3-butenyl)-L-thionolysinamide is then eluted with 10% aqueous pyridine.

After concentration, the product N-methyl-N-(3-oxacycloheptyl)-e-N-(1-imino-3-butenyl)-L-thionolysinamide is cooled in an ice bath and treated with one equivalent of 2-furanylacetyl chloride (1.4 g, 10 mmol) and stirred at room temperature for 24 hours. The reaction mixture is concentrated in vacuo and slurried with 50 ml methylene chloride. The methylene chloride is washed with water, concentrated in vacuo at 50 °C, and residue purified by chromatography to afford N-methyl-N-(3-oxacycloheptyl)-a-N-(2-furanylacetyl)-e-N-(1-imino-3-butenyl)-L-thionolysinamide.



Example 17

Ex-17a) e-(N-Z-Amino)-a-(N-boc-amino)hex-4-ene-oic acid (4.37 g, 12 mmol) is reacted with 4-(N-ethylamino)-1,2,3-triazole (1.40 g, 12.5 mmol) using the conditions to prepare as describe in **Ex-1a** in Example 1 to yield N-ethyl-N-(4-(1,2,3-triazolyl))-e-(N-Z-amino)-a-(N-Boc-amino)-hex-4-enamide.

Ex-17b) N-ethyl-N-(4-(1,2,3-triazolyl))-e-(N-Z-amino)-a-(N-Boc-amino)-hex-4-enamide is then subject to conditions to remove the Z protecting group as described in **Ex-1b** to N-ethyl-N-(4-(1,2,3-triazolyl))-e-amino-a-(N-Boc-amino)-hex-4-enamide.

Ex-17c) The resulting N-ethyl-N-(4-(1,2,3-triazolyl))-e-amino-a-(N-Boc-amino)-hex-4-enamide (3.79 g, 11 mmol) is reacted with chloro 1-(2-fluorocyclopropyl)formaldoxime (3.08 g) using the process described in **Ex-1c** to yield N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-(N-Boc-amino)-hex-4-enamide.

Ex-17d) N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-(N-Boc-amino)-hex-4-enamide is then subject to conditions to remove the Boc protecting group as described in **Ex-1d** to give N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-amino-hex-4-enamide.

Ex-17e) N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-amino-hex-4-enamide (4.71 g, 11 mmol) is treated with one equivalent trichloroethyl chloroformate (2.29 g, 11 mmol) and sodium carbonate in aqueous tetrahydrofuran under the conditions described by D. Gravel in Canadian Journal of Chemistry, 50, 3846, 1972 to give N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-N-(2,2,2-trichloroethoxyformyl)amino-hex-4-enamide.

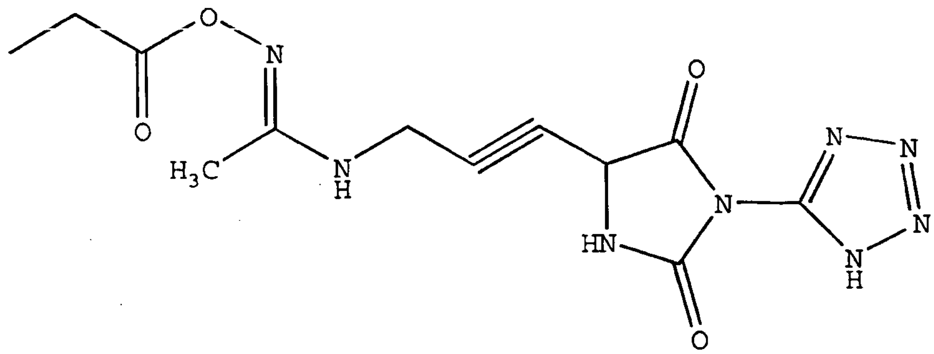
Ex-17f) N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-N-(2,2,2-trichloroethoxyformyl)amino-hex-4-enamide (6.29 g) is treated with Lawesson's Reagent under the conditions described in Chem. Reviews, 84, 17-30, 1984 and references cited therein, to yield N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-N-(2,2,2-trichloroethoxythionoformyl)amino-thionohex-4-enamide.

Ex-17g) N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-N-(2,2,2-trichloroethoxythionoformyl)amino-thionohex-4-enamide (5.26g, 10 mmol) is dissolved in acetic acid and treated with zinc dust (0.65g, 10 mmol). After stirring two hours, saturated aqueous sodium carbonate is added. The solids are removed by filtration. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-amino-thionohex-4-enamide is then eluted with 10% aqueous pyridine.

Ex-17h) N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-amino-thionohex-4-enamide (3.19 g, 9 mmol) is added to 50 mL of toluene in 100 mL reaction flask. After adding 1.71 g of p-toluenesulfonic acid and 2.17 g (14 mmol) 3-cyclopentenyl (thiomethyl)methyl ketone, the reaction mixture is refluxed with azeotropic distillation for complete removal of water using a Dean-Stark trap. After cooling, the solvent and excess 3-cyclopentenyl methoxymethyl ketone are removed in vacuo to give an essentially quantitative yield of the imine N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-N-(1-cyclopentyl-2-methylthioethenyl)amino-thionohex-4-enamide toluenesulfonate salt.

Ex-17i) N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-N-(1-(1-cyclopentyl-2-methylthioethenyl))amino-thionohex-4-enamide toluenesulfonate salt is dissolved in methanol and treated with 1.0M sodium cyanoborohydride in THF (9.1 mL) and potassium hydroxide using the conditions described by R. F. Borch in <u>Organic Synthesis</u>, 52, 124, 1972 to give, the product N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-N-(1-(1-cyclopentyl-2-methylthioethyl))amino-thionohex-4-enamide.

N-Ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-N-(1-(1-cyclopentyl-2-methylthioethyl))amino-thionohex-4-enamide (3.94g, 0.008 mol) is place in 20 ml of anhydrous THF containing 1.01 grams of triethylamine. After cooling in an ice bath, 2-cyanopropionyl chloride (0.99 g, 8.5 mmol) in 10 ml anhydrous THF is added over 20 minutes. After warming to room temperature, the solvent is removed in vacuo, 50 ml methylene chloride added along with 20 ml of water. The methylene chloride layer is separated, back washed with water, and concentrated to afford N-Ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-N-(1-(1-cyclopentyl-2-methylthioethyl))-2-cyanopropanamide-thionohex-4-enamide which can be purified if needed chromatographically.



Example 18

Ex-18a) e-(N-Z-Amino)-a-(N-Boc-amino)-pent-3-ynoic acid (3.83g, 11 mmol) is reacted with 5-aminotetrazole hydrochloride (1.40 g, 11.5 mmol) using the processed described in **Ex-1a** to yield N-(5-tetrazolyl)-e-(N-Z-amino)-a-(N-Boc-amino)-pent-3-ynamide.

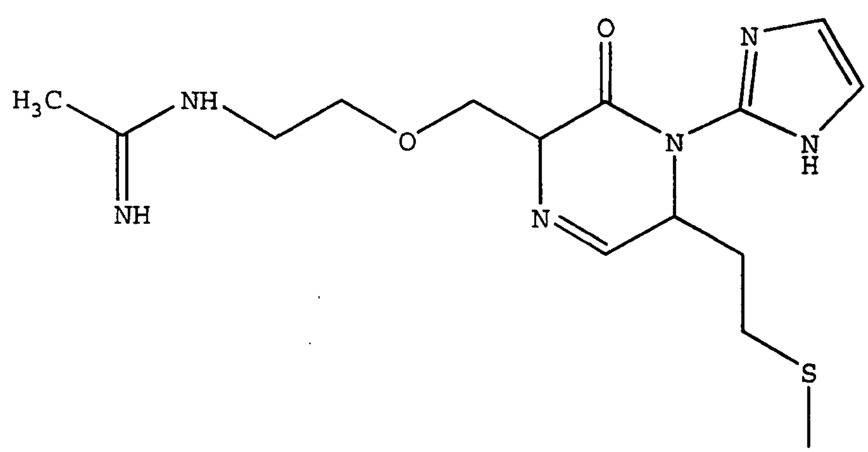
Ex-18b) N-(5-Tetrazolyl)-e-(N-Z-amino)-a-(N-Boc-amino)-pent-3-ynamide is then subject to conditions to remove the Z protecting group as described in **Ex-1b** to give N-(5-tetrazolyl)-e-amino-a-(N-Boc-amino)-pent-3-ynamide.

Ex-18c) The resulting N-(5-tetrazolyl)-e-amino-a-(N-Boc-amino)-pent-3-ynamide (3.10 g, 10 mmol) is reacted with chloroacetaldoxime (1.63 g) using the processed described in **Ex-1c** to yield N-(5-tetrazolyl)-e-N-(1-oximinoethyl)amino-a-(N-Boc-amino)-pent-3-ynamide.

Ex-18d) N-(5-tetrazolyl)-e-N-(1-oximinoethyl)amino-a-(N-Boc-amino)-pent-3-ynamide is dissolved in 30 mL of propionic anhydride containing 0.1 g of pyridine. After standing at room temperature for 2 hours, the reaction mixture is concentrated in vacuo to give N-(5-tetrazolyl)-e-N-(1-(O-propionyloximino)ethyl)amino-a-(N-Boc-amino)-pent-3-ynamide.

Ex-18e) N-(5-tetrazolyl)-e-N-(1-(O-propionyloximino)ethyl)amino-a-(N-Boc-amino)-pent-3-ynamide (3.96 g, 10 mmol) is dissolved in THF and cooled to -78°C. Two equivalents of lithium diisopropylamine (LDA) 2.0M solution (10 mL) is added dropwise over a period of 20 minutes. Phosgene (.998 g, 10.1 mmol) is added through a gas inlet tube over 30 minutes. After the mixture is allowed to warm to room temperature, 1 mL of water is added. The solvents are removed in vacuo and the product purified by chromatography to give 3-N-(5-tetrazolyl)-5-(3-(N-(1-(O-propionyloximino)ethyl)amino)prop-1-ynyl)-1-(N-boc)-hydantoin.

3-N-(5-tetrazolyl)-5-(3-(N-(1-(O-propionyloximino)ethyl)amino)prop-1-ynyl)-1-(N-boc)-hydantoin is then dissolved in trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give 3-N-(5-tetrazolyl)-5-(3-(N-(1-(O-propionyloximino)ethyl)amino)prop-1-ynyl)hydantoin trifluoroacetate.



Example 19

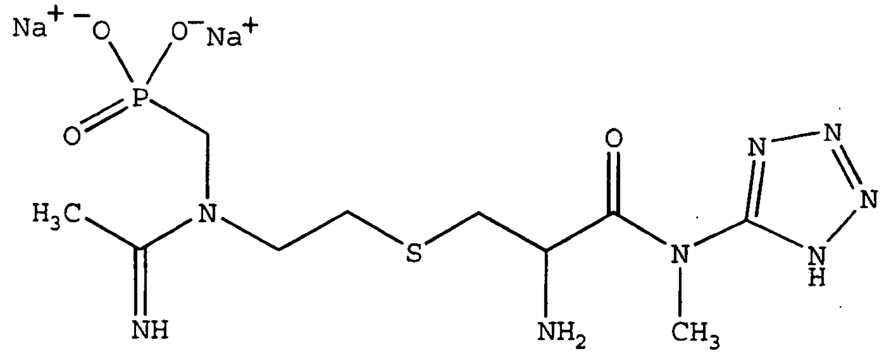
Ex-19a) a-(N-Boc)-O-(N-Z-2-aminoethyl)-L-serine (4.05 g, 11 mmol) is reacted with 2-aminoimidazole (0.95 g, 11.5 mmol) using the process described in **Ex-2a** to yield N-(2-imidazolyl)-a-(N-boc)-O-(N-Z-2-aminoethyl)-L-serinamide.

Ex-19b) N-(2-Imidazolyl)-a-(N-Boc)-O-(N-Z-2-aminoethyl)-L-serinamide is then subjected to conditions to remove the Z protecting group as described in **Ex-2b** to give N-(2-imidazolyl)-a-(N-Boc)-O-(2-aminoethyl)-L-serinamide.

Ex-19c) The resulting N-(2-imidazolyl)-a-(N-Boc)-O-(2-aminoethyl)-L-serinamide (3.22 g, 10 mmol) is reacted with methyl acetimidate hydrochloride (1.13 g) using the process in **Ex-2c** to yield N-(2-imidazolyl)-a-(N-boc)-O-(2-(N-(1-iminoethyl)amino)ethyl)-L-serinamide.

Ex-19d) N-(2-imidazolyl)-a-(N-boc)-O-(2-(N-(1-iminoethyl)amino)ethyl)-L-serinamide (3.54 g, 10 mmol) is dissolved in THF and cooled to -78°C. To the cooled mixture is added one equivalent of 2.0M lithium diisopropylamide solution (5 mL) over 30 minutes. One equivalent of 2-bromo-1,1-dimethoxy-4-thiomethylbutane (2.43 g, 10 mmol) dissolved in THF is added to the cooled mixture over 20 minutes. The mixture is allowed to warm to room temperature and 1 mL of water is added. The solvents are removed in vacuo and the product purified by chromatography to give N-(1-dimethoxy-4-thiomethyl-2-butyl)-N-(2-imidazolyl)-a-(N-boc)-O-(2-(N-(1-iminoethyl)amino)ethyl)-L-serinamide.

N-(1-dimethoxy-4-thiomethyl-2-butyl)-N-(2-imidazolyl)-a-(N-boc)-O-(2-(N-(1-iminoethyl)amino)ethyl)-L-serinamide (5 mmol) is then placed in 50 ml of aqueous 2N HCl. After standing at room temperature until the t-butoxycarbonyl and methoxy groups are removed, the reaction mixture is then concentrated in vacuo to give 1-N-(2-imidazolyl)-3-(2-(N-(1-iminoethyl)amino)ethoxy)methyl)-6-(2-methiothioethyl)-2-oxo-3,6-dihydropyrazine trihydrochloride.



Example 20

Ex-20a) a-(N-Boc)-S-(N-Z-aminoethyl)-L-cysteine (4.22 g, 11 mmol) is reacted with 5-methylaminotetrazole hydrochloride (1.53 g, 11.5 mmol) using the process described in **Ex-2a** to yield N-methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(N-Z-aminoethyl)-L-cysteinamide.

Ex-20b) N-Methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(N-Z-aminoethyl)-L-cysteinamide is then subject to conditions to remove the Z protecting group as described in **Ex-2b** to give N-methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(aminoethyl)-L-cysteinamide.

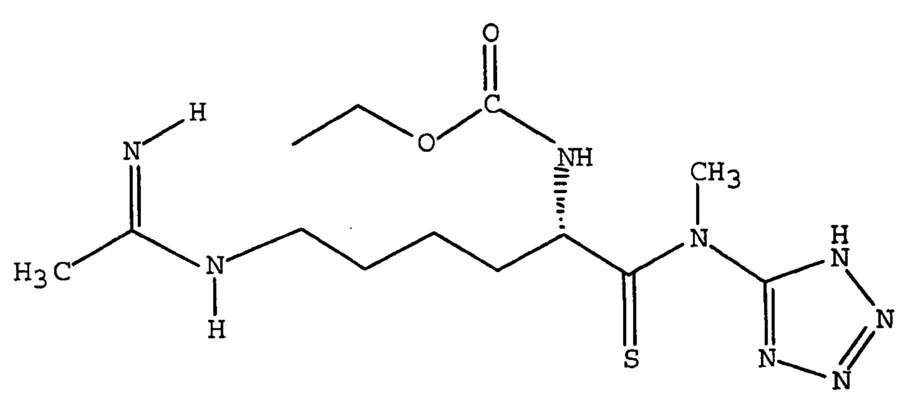
Ex-20c) The resulting N-methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(aminoethyl)-L-cystinamide (2.30 g, 10 mmol) is added to 50 mL of water in a 200 mL reaction flask and the pH adjusted to 6-7 with hydrochloric acid. After forming an equilibrium concentration of the imine, N-methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(2-(N-phosphonomethyleneamino)ethyl)-L-cysteinamide, by addition of 10 mmol of disodium formylphosphonate while maintaining a pH of 6-7, 50 ml of methanol is added. The reaction mixture is treated with 1.0M sodium cyanoborohydride in THF (40 mL). The excess borohydride is destroyed, the reaction mixture concentrated to remove organic solvents, and the residue purified by passing it through a reverse

phase chromatographic column to give the product N-methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(2-(N-phosphonomethylamino)ethyl)-L-cysteinamide.

Ex-20d) N-methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(2-(N-phosphonomethylamino)ethyl)-L-cysteinamide (8 mmol) is reacted with methyl acetimidate hydrochloride (1.75 g) using the process described in **Ex-2c** to yield N-methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(2-(N-phosphonomethyl-N-(1-iminoethyl)amino)ethyl)-L-cysteinamide.

N-methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(2-(N-phosphonomethyl-N-(1-iminoethyl)amino)ethyl)-L-cysteinamide is then placed in 50 ml of aqueous 2N HCl. After standing at room temperature until the t-butoxycarbonyl group is removed, the reaction mixture is then concentrated in vacuo to give N-methyl-N-(5-tetrazolyl)-S-(2-(N-phosphonomethyl-N-(1-iminoethyl)amino)ethyl)-L-cysteinamide hydrochloride.

N-methyl-N-(5-tetrazolyl)-S-(2-(N-phosphonomethyl-N-(1-iminoethyl)amino)ethyl)-L-cysteinamide hydrochloride (5 mmol) is placed in 50 ml water and stirred vigorously with a mixture of 5mmol of N,N-dimethyloctadecylamine in 75 ml of toluene. The aqueous layer is separated and two equivalents of NaOH (10 mmol) is added to generate the disodium salt of N-methyl-N-(5-tetrazolyl)-S-(2-(N-phosphonomethyl-N-(1-iminoethyl)amino)ethyl)-L-cysteinamide.



Example 21

Ex-21a) e-(N-Z-Amino)-a-(N-Boc-amino)-hexanoic acid (4.39 g, 12 mmol) is reacted with 5-(N-methylamino)tetrazole (1.06 g, 12.5 mmol) using the conditions to prepare on Page 94 in Example 1 to yield N-methyl-N-(5-tetrazolyl)-e-(N-Z-amino)-a-(N-Boc-amino)hexanamide.

Ex-21b) N-Methyl-N-(5-tetrazolyl)-e-(N-Z-amino)-a-(N-Boc-amino)hexanamide is then subject to conditions to remove the Z protecting group as described in **Ex-1b** to yield N-methyl-N-(5-tetrazolyl)-e-(amino)-a-(N-Boc-amino)hexanamide.

Ex-21c) The resulting N-methyl-N-(5-tetrazolyl)-e-(amino)-a-(N-Boc-amino)hexanamide (3.73 g, 11 mmol) is reacted with methyl acetimidate hydrochloride (2.49 g) using the process in **Ex-2c** to yield N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-a-(N-Boc-amino)hexanamide.

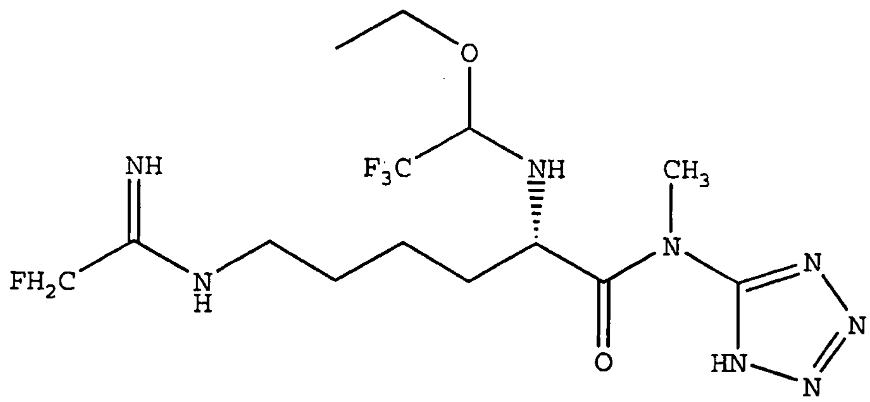
Ex-21d) N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-a-(N-Boc-amino)hexanamide is then subject to conditions to remove the Boc protecting group as described in **Ex-2d** to give N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-a-aminohexanamide.

Ex-21e) N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-a-aminohexanamide (2.89 g, 11 mmol) is treated with one equivalent trichloroethyl chloroformate (2.29 g) and sodium carbonate in aqueous tetrahydrofuran under the conditions described by D. Gravel in Canadian Journal of Chemistry 50, 3846, 1972 to give N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-a-(N-(2,2,2-trichloroethoxyformyl))aminohexanamide.

Ex-21g) N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-a-(N-(2,2,2-trichloroethoxyformyl))aminohexanamide (4.65 g) is treated with Lawesson's Reagent under the conditions described in Chem. Reviews, 84, 17-30, 1984 and references cited therein to yield N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-a-(N-(2,2,2-trichloroethoxythionoformyl))aminothionohexanamide.

Ex-21g) N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-a-(N-(2,2,2-trichloroethoxythionoformyl))aminothionohexanamide (4.70 g, 10 mmol) is dissolved in acetic acid and treated with zinc dust (0.65g, 10 mmol). After stirring two hours, saturated aqueous sodium carbonate is added. The solids are removed by filtration. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-a-aminothionohexanamide is then eluted with 10% aqueous pyridine.

N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-a-aminothionohexanamide (2.51 g, 9 mmol) is place in 20 ml of anhydrous THF containing 1.01 grams of triethylamine. After cooling to -78 °C, ethyl chloroformate (0.98 g, 9 mmol) in 10 ml anhydrous THF is added over 20 minutes. After warming to room temperature, the solvent is removed in vacuo, 50 ml methylene chloride added along with 20 ml of water. The methylene chloride layer is separated, back washed with water, and concentrated to afford N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-a-((N-ethoxycarbonyl)amino)thionohexanamide.



Example 22

Ex-22a) e-(N-Z-Amino)-a-(N-Boc-amino)hexanoic acid (4.39 g, 12 mmol) is reacted with 5-(N-methylamino)tetrazole (1.06 g, 12.5 mmol) using the process in **Ex-2a** to yield N-methyl-N-(5-tetrazolyl)-e-(N-Z-amino)-a-(N-Boc-amino)hexanamide.

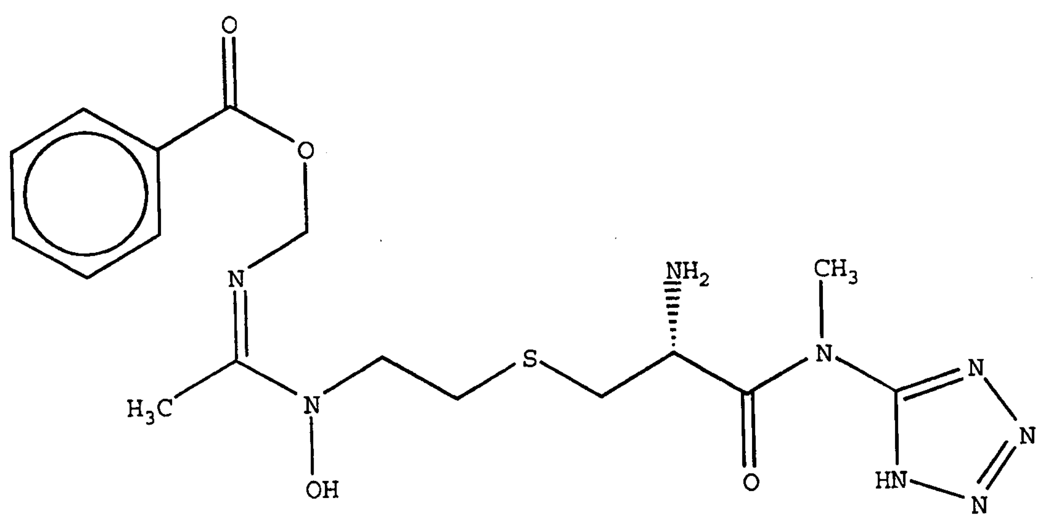
Ex-22b) N-Methyl-N-(5-tetrazolyl)-e-(N-Z-amino)-a-(N-Boc-amino)hexanamide is then subject to conditions to remove the Z protecting group as described in **Ex-2b** to give N-methyl-N-(5-tetrazolyl)-e-(amino)-a-(N-Boc-amino)-hexanamide.

Ex-22c) The resulting N-methyl-N-(5-tetrazolyl)-e-(amino)-a-(N-Boc-amino)hexanamide (3.72 g, 11 mmol) is reacted with methyl 2-fluoroacetimidate hydrochloride (2.07) using the process in **Ex-2c** to yield N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-(N-Boc-amino)hexanamide.

Ex-22d) N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-(N-Boc-amino)hexanamide is then subject to conditions to remove the Boc protecting group as described in **Ex-2d** to N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-aminohexanamide.

Ex-22e) N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-aminohexanamide (2.95 g, 10 mmol) is placed in 20 mL of anhydrous THF containing 1.01 grams of triethylamine. After cooling to -78°C, trifluoroacetic anhydride (2.17 g, 10.3 mmol) in 10 mL anhydrous THF is added over 20 minutes. After warming to room temperature, the solvent is removed in vacuo to afford N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-trifluoroacetamidohexanamide trifluoroacetate.

N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-trifluoroacetamidohexanamide trifluoroacetate (9 mmol) is dissolved in ethanol and treated with two equivalents of sodium borohydride (0.74 g, 20 mmol). After stirring several hours, the ethanol is removed in vacuo. Upon completion, 50 mL methylene chloride is added along with 20 mL of water. The methylene chloride layer is separated, back washed with water, dried over $MgSO_4$, and concentrated to afford N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-(N-(2,2,2-trifluoro-1-ethoxyethyl))aminohexanamide.

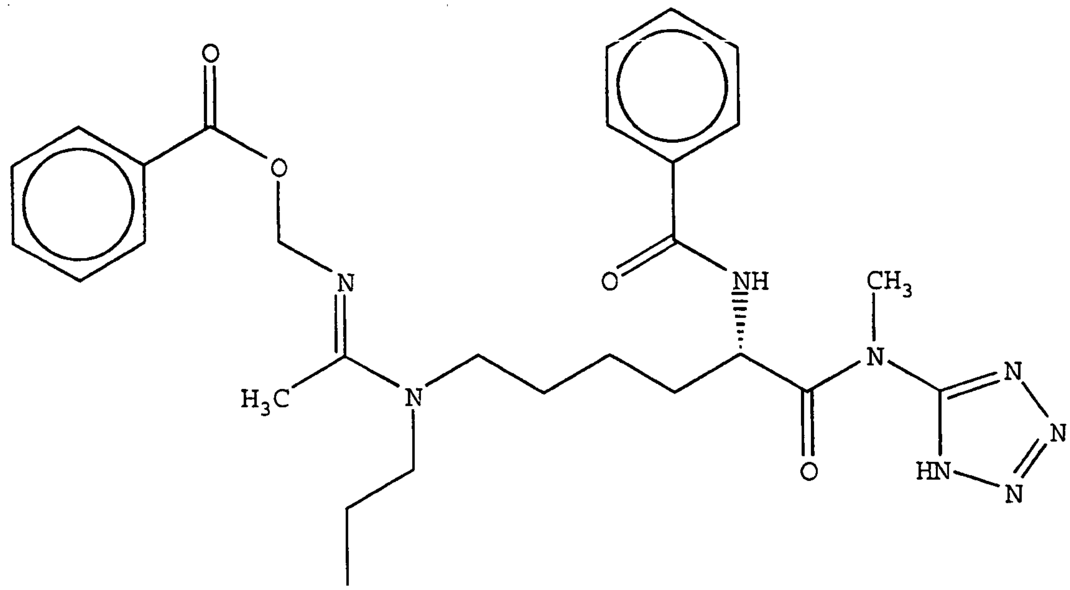


Example 23

Ex-23a) a-(N-Z)-S-(N-hydroxy-2-aminoethyl)-L-cysteine methyl ester (3.14 g, 10 mmol) is treated with methyl (N-(benzoyloxymethyl)acetimidate hydrochloride (4.14 g) as described in **Ex-2c** to give a-(N-Z)-S-(2-(1-(N-(benzoyloxymethyl)imino)ethyl)-N-hydroxy)aminoethyl)-L-cysteine methyl ester.

Ex-23b) a-(N-Z)-S-(2-(1-(N-(benzoyloxymethyl)imino)ethyl)-N-hydroxy)aminoethyl)-L-cysteine methyl ester (4.49 g, 9 mmol) is dissolved in DMF and treated with N-methyl-5-amino-tetrazole (0.93 g, 9.5 mmol). The mixture is heated until replacement of the methoxy is observed. Upon completion, the reaction mixture is concentrated. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-methyl-N-(5-tetrazolyl)-a-(N-Z)-S-(2-(1-(N-(benzoyloxymethyl)imino)ethyl)-N-hydroxy)aminoethyl)-L-cysteinamide.

N-methyl-N-(5-tetrazolyl)-a-(N-Z)-S-(2-(1-(N-(benzoyloxymethyl)imino)ethyl)-N-hydroxy)aminoethyl)-L-cysteinamide is then subject to conditions to remove the Z protecting group as described in **Ex-2b** to give N-methyl-N-(5-tetrazolyl)-S-(2-(1-(N-(benzoyloxymethyl)imino)ethyl)-N-hydroxy)aminoethyl)-L-cysteinamide.



Example 24

Ex-24a) a-(N-Z)-e-(N-Boc)-L-Lysine (3.66 g, 10 mmol) is treated with N-methyl-5-amino-tetrazole (0.89 g, 10.5 mmol) using the conditions to prepare **Ex-3a** to yield N-methyl-N-(5-tetrazolyl)-a-(N-Z)-e-(N-Boc)-L-Lysine.

Ex-24b) N-methyl-N-(5-tetrazolyl)-a-(N-Z)-e-(N-Boc)-L-Lysine is then subject to conditions to remove the Boc protecting group as described in **Ex-3b** to give N-methyl-N-(5-tetrazolyl)-a-(N-Z)-L-Lysine.

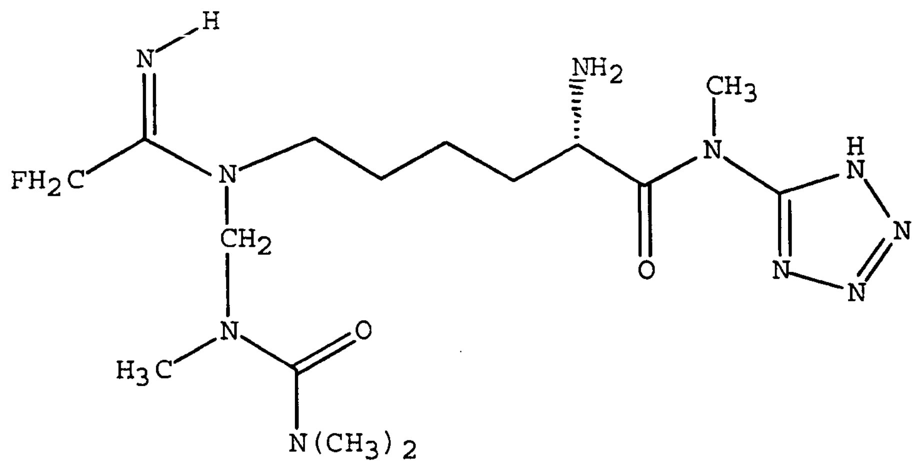
Ex-24c) N-Methyl-N-(5-tetrazolyl)-a-(N-Z)-L-Lysine (3.37 g, 10 mmol) is added to 50 mL of toluene in 100 mL reaction flask. After adding 1.89 g of p-toluenesulfonic acid and 0.93 g (16 mmol) propionaldehyde the reaction mixture is refluxed with azeotropic distillation for complete removal of water using a Dean-Stark trap. After cooling, the solvent is removed in vacuo to give the iminium salt, N-methyl-N-(5-tetrazolyl)-a-(N-Z)-e-N-(1-propylene)-L-Lysine p-toluenesulfonate.

Ex-24d) N-methyl-N-(5-tetrazolyl)-a-(N-Z)-e-N-(1-propylene)-L-Lysine p-toluenesulfonate (9 mmol) is dissolved in methanol and treated with 1.0M sodium cyanoborohydride in THF (19 mL) and potassium hydroxide using the conditions and work-up described by R. F. Borch in Organic Synthesis, 52, 124, 1972 to give the product, N-methyl-N-(5-tetrazolyl)-a-(N-Z)-e-N-(1-propyl)-L-Lysine.

Ex-24e) N-methyl-N-(5-tetrazolyl)-a-(N-Z)-e-N-(1-propyl)-L-Lysine (3.27 g, 8 mmol) is treated with methyl (N-(benzoyloxymethyl)acetimidate hydrochloride (3.70 g) as described in **Ex-2c** to give N-methyl-N-(5-tetrazolyl)-a-(N-Z)-e-N-(2-(1-(N-(benzoyloxymethyl)imino)ethyl))- e-N-(1-propyl)-L-Lysine.

Ex-24f) N-methyl-N-(5-tetrazolyl)-a-(N-Z)-e-N-(2-(1-(N-(benzoyloxymethyl)imino)ethyl))- e-N-(1-propyl)-L-Lysine is then subject to conditions to remove the Z protecting group as in **Ex-2b** to give N-methyl-N-(5-tetrazolyl)-e-N-(2-(1-(N-(benzoyloxymethyl)imino)ethyl))- e-N-(1-propyl)-L-Lysine.

N-methyl-N-(5-tetrazolyl)-e-N-(2-(1-(N-(benzoyloxymethyl)imino)ethyl))- e-N-(1-propyl)-L-Lysine (3.20 g, 7 mmol) is placed in 20 mL of anhydrous THF containing 1.01 grams of triethylamine. After cooling to -78°C, benzoyl chloride (1.01 g, 7.2 mmol) in 10 mL anhydrous THF is added over 20 minutes. After warming to room temperature, the solvent is removed in vacuo, 50 mL methylene chloride is added along with 20 mL of water. The methylene chloride layer is separated, back washed with water, dried over $MgSO_4$, and concentrated to afford N-methyl-N-(5-tetrazolyl)- a-N-benzoyl- e-N-(2-(1-(N-(benzoyloxymethyl)imino)ethyl))- e-N-(1-propyl)-L-Lysine.



EXAMPLE 25

Ex-25a) To a stirring DMF solution of ε-pnZ-α-Boc-L-Lysine (4.50 g, 10.0 mmol), 1-(4-nitrobenzyloxymethyl)-5-methylaminotetrazole (2.77 g, 10.5 mmol), 2.53 g triethylamine (0.025 mol) and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl]ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-ε-pnZ-α-Boc-L-Lysinamide.

Ex-25b) N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-ε-pnZ-α-Boc-L-Lysinamide is then dissolved in 25 mL. anhydrous trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is concentrated to dryness in vacuo, aqueous sodium carbonate added to neutralize residual acid, and the aqueous solution extracted with methylene chloride to yield N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-ε-pnZ-L-Lysinamide.

Ex-25c) N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-ε-pnZ-L-Lysinamide (4.57 g, 8.0 mmol) is placed in admixture with tetrahydrofuran (50 mL) and phthalic anhydride (1.19 g, 8.0 mmol) and heated at reflux until the reaction was complete. Removal of the tetrahydrofuran afforded the phthalimide of N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-ε-pnZ-L-Lysinamide.

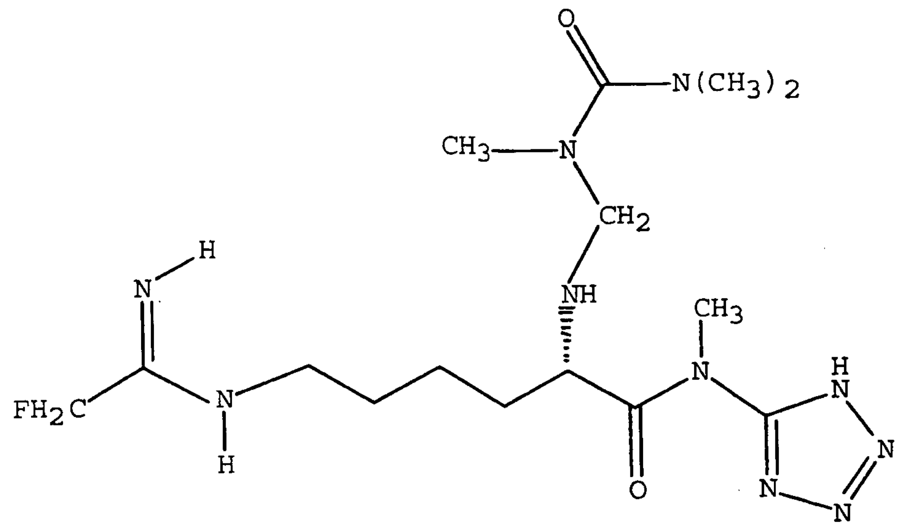
Ex-25d) Phthalimide is thoroughly dried and dissolved in 25 mL of anhydrous THF. To the THF solution cooled to -78 °C, is added 1.1 equivalents of diisopropylamine followed by 1 equivalent on n-butyl lithium in hexane. Subsequently, 1.1 equivalents of N-chloromethyl-N,N'N'-trimethylurea was added. After warming to room temperature, the reaction mixture is filtered to remove the precipitant and concentrated in vacuo to give N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-α-N-phthaloyl-ε-pnZ-ε-N-(N,N'N'-trimethylureido-N-methylene)-L-Lysinamide.

Ex-25e) N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-α-N-phthaloyl-ε-pnZ-ε-N-(N,N'N'-trimethylureido-N-methylene)-L-Lysinamide dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the pnZ-functions generating the amino product N-methyl-N-(5-(tetrazolyl)-α-N-phthaloyl-ε-N-(N,N'N'-trimethylureido-N-methylene)-L-Lysinamide.

Ex-25f) To a 125 mL flask was added 2.36 g (0.005 mol) of N-methyl-N-(5-(tetrazolyl)-α-N-phthaloyl-ε-N-(N,N'N'-trimethylureido-N-methylene)-L-Lysinamide is converted to N-methyl-N-(5-(tetrazolyl)-α-N-phthaloyl-ε-N-(2-fluoro-1-iminoethyl)-ε-N-(N,N'N'-trimethylureido-N-methylene)-L-Lysinamide as described in **Ex-15c.**

N-methyl-N-(5-(tetrazolyl)-α-N-phthaloyl-ε-N-(2-fluoro-1-iminoethyl)-ε-N-(N,N'N'-trimethylureido-N-methylene)-L-Lysinamide (1.59 g, 0.003 mol) is

dissolved in 25 mL methanol and hydrazine (0.96 g, 0.003 mol) added. After refluxing for 6 hours, the methanol is removed, aqueous 10 % hydrochloric acid added to the residue in an ice bath until the pH was 3 to 4, and the precipitated hydrazide removed by filtration. The aqueous solution is concentrated in vacuo to give the dihydrochloride of N-methyl-N-(5-(tetrazolyl)-ε-N-(2-fluoro-1-iminoethyl)-ε-N-(N,N'N'-trimethylureido-N-methylene)-L-Lysinamide.



EXAMPLE 26

Ex-26a) To a stirring DMF solution of ε-Boc-α-pnZ-L-Lysine (4.50 g, 10.0 mmol), 1-(4-nitrobenzyloxymethyl)-5-methylaminotetrazole (2.77 g, 10.5 mmol), 2.53 g triethylamine (0.025 mol) and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-ε-Boc-α-pnZ L-Lysinamide.

Ex-26b) N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-ε-Boc-α-pnZ -L-Lysinamide is then dissolved in 25 mL. anhydrous trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is concentrated to dryness in vacuo, aqueous sodium carbonate added to neutralize residual acid, and the aqueous solution extracted with methylene chloride to yield N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-α-pnZ-L-Lysinamide.

Ex-26c) N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-α-pnZ-L-Lysinamide (4.57 g, 8.0 mmol) is placed in admixture with tetrahydrofuran (50 mL) and phthalic anhydride (1.19 g, 8.0 mmol) and heated at reflux until the reaction is complete. Removal of the tetrahydrofuran afforded the phthalimide of N-methyl-N-(5-(4-nitrobenzyloxymethyl) tetrazolyl)-α-pnZ-L-Lysinamide.

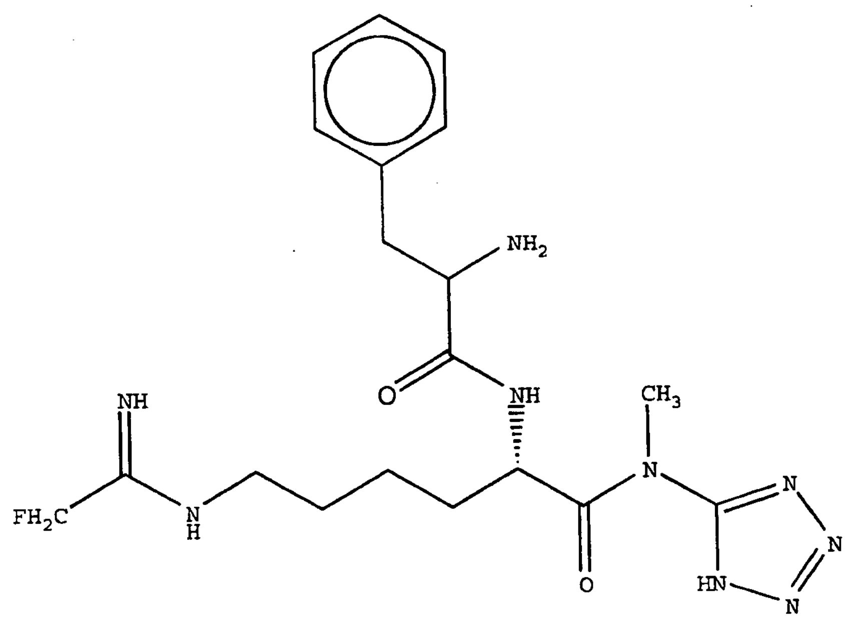
Ex-26d) Phthalimide is thoroughly dried and dissolved in 25 mL of anhydrous THF. To the THF solution cooled to -78 °C, is added 1.1 equivalents of diisopropylamine followed by 1 equivalent on n-butyl lithium in hexane. Subsequently, 1.1 equivalents of N-chloromethyl-N,N'N'-trimethylurea was added. After warming to room temperature, the reaction mixture is filtered to remove the precipitant and concentrated in vacuo to give N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-ε-N-phthaloyl-α-pnZ-α-N-(N,N'N'-trimethylureido-N-methylene)-L-Lysinamide.

Ex-26e) N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-ε-N-phthaloyl-α-pnZ-α-N-(N,N'N'-trimethylureido-N-methylene)-L-Lysinamide is dissolved in 25 mL methanol and one equivalent of hydrazine added. After refluxing for 6 hours, the methanol is removed, aqueous 10 % hydrochloric acid added to the residue in an ice bath until the pH was 7, and the precipitated hydrazide removed by filtration. The aqueous solution is concentrated in vacuo to give N-methyl-N-(5-(4-

nitrobenzyloxymethyl)tetrazolyl)-α-pnZ-α-N-(N,N'N'-trimethylureido-N-methylene)-L-Lysinamide hydrochloride.

Ex-26f) The N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-α-pnZ-α-N-(N,N'N'-trimethylureido-N-methylene)-L-Lysinamide is converted to N-methyl-N-(5-(4-nitrobenzyloxymethyl) tetrazolyl)-α-pnZ-ε-N-(2-fluoro-1-iminoethyl)-α-N-(N,N'N'-trimethylureido-N-methylene)-L-Lysinamide as described in **Ex-15c.**

N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-α-pnZ-ε-N-(2-fluoro-1-iminoethyl)-α-N-(N,N'N'-trimethylureido-N-methylene)-L-Lysinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the pnZ-functions generating the amino product N-methyl-N-(5-tetrazolyl)-ε-N-(2-fluoro-1-iminoethyl)-α-N-(N,N'N'-trimethylureido-N-methylene)-L-Lysinamide.



Example 27

Ex-27a) e-(N-Z-Amino)-a-(N-Boc-amino)hexanoic acid (3.66 g, 10 mmol) is reacted with 5-(N-methylamino)tetrazole (0.89 g, 10.5 mmol) using the process described in **Ex-2a** to yield N-methyl-N-(5-tetrazolyl)-e-(N-Z-amino)-a-(N-Boc-amino)hexanamide.

Ex-27b) N-Methyl-N-(5-tetrazolyl)-e-(N-Z-amino)-a-(N-Boc-amino)hexanamide is then subject to conditions to remove the Z protecting group as described in **Ex-2b** to N-methyl-N-(5-tetrazolyl)-e-(amino)-a-(N-Boc-amino)hexanamide.

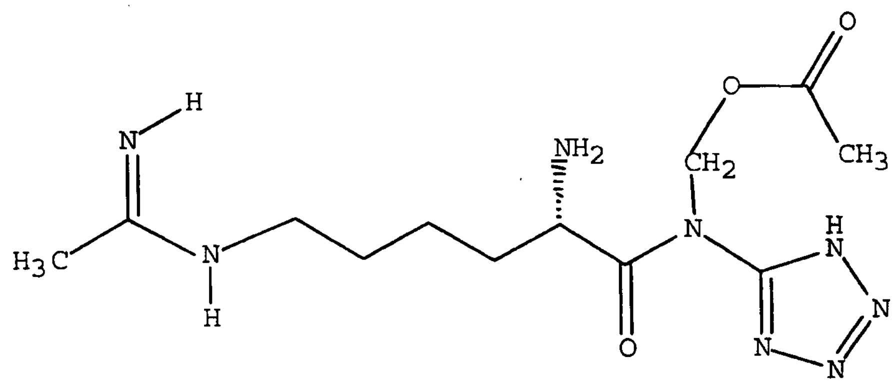
Ex-27c) The resulting N-methyl-N-(5-tetrazolyl)-e-(amino)-a-(N-Boc-amino)hexanamide (3.01 g, 9 mmol) is reacted with methyl 2-fluoroacetimidate hydrochloride (1.67 g) using the process described in **Ex-2c** in Example 2 to yield N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-(N-Boc-amino)hexanamide.

Ex-27d) N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-(N-Boc-amino)hexanamide is then subject to conditions to remove the Boc protecting group as described in **Ex-2d** to give N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-aminohexanamide.

Ex-27e) To a stirring DMF solution of N-Boc-phenylalanine (2.25 g, 8.5 mmol), N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-aminohexanamide (2.17 g, 8 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-methyl-N-(5-

tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-(N-(N-Boc-phenylalaninyl)amino)hexanamide.

N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-(N-(N-Boc-phenylalaninyl)amino)hexanamide is then subject to conditions to remove the Boc protecting group as described in **Ex-2d** to give N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-(N-(phenylalaninyl)amino)hexanamide.



EXAMPLE 28

Ex-28a) ε-Boc-α-pnZ-L-Lysine (4.50 g, 10.0 mmol) and 1-(4-nitrobenzyloxymethyl)aminotetrazole (2.62 g, 10.5 mmol) was converted to N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-ε-Boc-α-pnZ-L-Lysinamide analogous to that described in Example 26.

Ex-28b) N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-ε-Boc-α-pnZ-L-Lysinamide is then converted to N-(5-(4-nitrobenzyloxy methyl)tetrazolyl)-α-pnZ-L-Lysinamide analogous to that described in Example 26.

Ex-28c) N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-α-pnZ-L-Lysinamide (4.57 g, 8.0 mmol) is then converted to the phthalimide of N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-α-pnZ-L-Lysinamide analogous to that described in Example 26.

Ex-28d) Phthalimide is thoroughly dried and dissolved in 25 mL of anhydrous THF. To the THF solution cooled to -78 °C, is added 1.1 equivalents of diisopropylamine followed by 1 equivalent on n-butyl lithium in hexane. Subsequently, 1.1 equivalents of chloromethyl acetate was added. After warming to room temperature, the reaction mixture is filtered to remove the precipitant and concentrated in vacuo to give N-acetoxymethyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-ε-N-phthaloyl-α-pnZ-L-Lysinamide

Ex-28e) N-acetoxymethyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-ε-N-phthaloyl-α-pnZ-L-Lysinamide was converted to N-acetoxymethyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-α-pnZ-L-Lysinamide analogous to that described in Example 26.

Ex-28f) N-acetoxymethyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-α-pnZ-L-Lysinamide is converted to N-acetoxymethyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-α-pnZ-ε-N-(iminoethyl)-L-Lysinamide as described in **Ex-2c.**

N-acetoxymethyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-α-pnZ-ε-N-(iminoethyl)-L-Lysinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the pnZ-functions generating the amino product N-acetoxymethyl-N-(5-tetrazolyl)-ε-N-(iminoethyl)-L-Lysinamide.

Biological Data

The subject compounds of formula (I) are expected to be found to inhibit nitric oxide synthase and posses useful pharmacological properties as demonstrated in one or more of the following assays:

Citrulline Assay for Nitric Oxide Synthase

NOS activity can be measured by monitoring the conversion of L-[2,3-^{3}H]-arginine to L-[2,3-^{3}H]-citrulline. Mouse inducible NOS (miNOS) can be prepared from an extract of LPS-treated mouse RAW 264.7 cells and rat brain constitutive NOS (rnNOS) can be prepared from an extract of rat cerebellum. Both preparations can be partially purified by DEAE-Sepharose chromatography. Enzyme (10 μL) can be added to 40 μL of 50 mM Tris (pH 7.6) and the reaction initiated by the addition of 50 μL of a solution containing 50 mM Tris (pH 7.6), 2.0 mg/mL bovine serum albumin, 2.0 mM DTT, 4.0 mM $CaCl_2$, 20 μM FAD, 100 μM tetrahydrobiopterin, 2.0 mM NADPH and 60 μM L-arginine containing 0.9 μCi of L-[2,3-^{3}H]-arginine. For constitutive NOS, calmodulin is included at a final concentration of 40 nM. Following incubation at 37°C for 15 minutes, the reaction can be terminated by addition of 300 μL cold buffer containing 10 mM EGTA, 100 mM HEPES (pH 5.5) and 1.0 mM L-citrulline. The [^{3}H]-citrulline can be separated by chromatography on Dowex 50W X-8 cation exchange resin and radioactivity quantified with a liquid scintillation counter.

Raw Cell Nitrite Assay

RAW 264.7 cells can be plated to confluency on a 96-well tissue culture plate grown overnight (17h) in the presence of LPS to induce NOS. A row of 3-6 wells can be left untreated and served as controls for subtraction of nonspecific background. The media can be removed from each well and the cells washed twice with Kreb-Ringers-Hepes (25mM, pH 7.4) with 2 mg/ml glucose. The cells are then placed on ice and incubated with 50mL of buffer containing L-arginine (30mM) +/- inhibitors for 1h. The assay can be initiated by warming the plate to 37°C in a water bath for 1h. Production of nitrite by intracellular iNOS will be linear with time. To terminate the cellular assay, the plate of cells can be placed on ice and the nitrite-containing buffer removed and analyzed for nitrite using a previously published fluorescent determination for nitrite. T. P. Misko et al, Analytical Biochemistry, 214, 11-16 (1993).

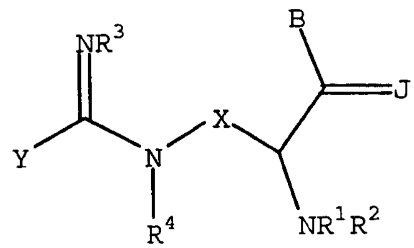
In Vivo Assay

Rats can be treated with an intraperitoneal injection of 10mg/kg of endotoxin (LPS) with or without oral administration of the nitric oxide synthase inhibitors. Plasma nitrites can be measured 5 hours post-treatment. The results can be used to show that the administration of the nitric oxide synthase inhibitor decreases the rise in plasma nitrites, a reliable indicator of the production of nitric oxide induced by endotoxin.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. A compound having the formula



and pharmaceutically acceptable salts and prodrugs,

wherein:

J is O or S;

R^1 and R^2 are independently selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, hydroxyl, sulfhydryl, OR^6, SR^6, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, $CH_2SO_3^- M^+$, $CH_2CH_2SO_3^- M+$, $CH_2PO_3^{-2}\ 2M^+$, $CH_2CH_2PO_3^{-2}\ 2M^+$, $CH(OR^6)CF_3$, $S(O)R^{13}$, SO_2R^{13}, $P(O)(R^{30})_2$, $P(O)(R^{30})_3$, $C(O)R^{15}$, $C(S)R^{15}$, $CH_2OC(O)R^{15}$, $CH_2NR^{19}C(O)R^{15}$, $CH_2NR^{19}C(S)R^{15}$, $CH_2SC(O)R^{15}$, $CH_2SC(S)R^{15}$, $CH_2OC(O)GR^{15}$, $CH_2NR^{19}C(O)GR^{15}$, $CH_2NR^{19}C(S)GR^{15}$, $CH_2OC(S)GR^{15}$, $CH_2SC(S)GR^{15}$, OSO_2R^{13}, $OS(O)R^{13}$, $OC(S)R^{15}$, $SC(S)R^{15}$, $OC(S)GR^{15}$, $SC(S)GR^{15}$,

$OC(O)R^{15}$, $SC(O)R^{15}$, $OC(O)GR^{15}$, $SC(O)GR^{15}$, and $R^{19}(R^{20})CH$; all, except hydrogen, alkyl, lower alkenyl, lower alkynyl, hydroxyl and sulfhydryl, may be optionally substituted by one or more alkyl, haloalkyl, aryl, hydroxyl, thiol, amino, alkylamino, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, carboxy, aryloxy, heteroaryloxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups; provided that only one of R^1 and R^2 can be hydrogen, alkyl, alkenyl and alkynyl unless J is S; when J is O, R^3 and R^4 are independently selected to be other than hydrogen, lower alkyl, lower alkenyl, lower alkynyl, OR^6 wherein R^6 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl, SO_2R^{13} wherein R^{13} is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, and $C(O)R^{15}$, wherein R^{15} is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl, or B is NR^5R^{11} wherein R^5 is selected from other than the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl and aryl;

R^1 and R^2 can be taken together to form imines containing the substituent of formula $R^{19}(R^{20})C$=;

R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, hydroxyl, sulfhydryl, OR^6, SR^6, $CH_2SO_3^- M^+$, $CH_2CH_2SO_3^- M+$, $CH_2PO_3^{-2}\ 2M^+$, $CH_2CH_2PO_3^{-2}\ 2M^+$, $S(O)R^{13}$, SO_2R^{13}, $P(O)(R^{30})_2$, $P(O)(R^{30})_3$, $C(O)R^{15}$, $C(S)R^{15}$, $CH_2OC(O)R^{15}$, $CH_2NR^{19}C(O)R^{15}$, $CH_2NR^{19}C(S)R^{15}$, $CH_2SC(O)R^{15}$, $CH_2SC(S)R^{15}$, $CH_2OC(O)GR^{15}$, $CH_2NR^{19}C(O)GR^{15}$, $CH_2NR^{19}C(S)GR^{15}$, $CH_2OC(S)GR^{15}$, $CH_2SC(S)GR^{15}$, OSO_2R^{13}, $OS(O)R^{13}$, $OC(S)R^{15}$, $SC(S)R^{15}$, $OC(S)GR^{15}$, $SC(S)GR^{15}$,

$OC(O)R^{15}$, $SC(O)R^{15}$, $OC(O)GR^{15}$, and $SC(O)GR^{15}$; provided that when J is O, R^6 cannot be lower alkyl, lower alkenyl, lower alkynyl or aryl and R^3 or R^4 cannot be OR^6; R^{13} cannot be lower alkyl, lower alkenyl, lower alkynyl or aryl when R^3 or R^4 is SO_2R^{13}, R^{15} cannot be lower alkyl, lower alkenyl, lower alkynyl or aryl when R^3 or R^4 is COR^{15}; provided only one of R^3 and R^4 can be hydrogen, lower alkyl, lower alkenyl, or lower alkynyl unless R^1 and R^2 are independently selected from other than hydrogen, alkyl, lower alkenyl, and lower alkynyl or B is NR^5R^{11} wherein R^5 is selected from other than the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl and aryl;

G is selected from the group consisting of O, S, CH_2, CHR^{15}, $C(R^{15})_2$, NH, and NR^{15};

R^6 is selected from the group consisting of hydroxyalkyl, heteroaryloxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl,

aralkoxysulfonylalkyl, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and alkylpolyhydroxy;

R^{13} is selected from the group consisting of aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxyusulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and alkylpolyhydroxy;

R^{15} is selected from the group consisting of hydrido, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl,

dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxyusulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and alkylpolyhydroxy;

M^+ is a pharmaceutically acceptable cation;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, and $-(CH_2)_pQ(CH_2)_r-$ wherein p is 1 to 3, r is 1 to 3 and Q is oxygen, C=O, and $S(O)_t$ wherein t is 0 to 2, groups which may be optionally substituted with one or more alkyl, alkoxy, hydroxy, sulfhydryl, halogen, trifluoromethyl, nitro, cyano, amino, $P(O)R^{21}$ wherein R^{21} is hydroxyl or alkyl which may be optionally substituted with one or more alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, amino, carboxy, or $N(R^{12})_n$ wherein n is 1 to 2 and R^{12} is hydrogen, oxy, hydroxyl or alkyl which may be optionally substituted with one or more alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, or amino; or

X is $-(CH_2)_sA(CH_2)_v-$ wherein s is O to 2, v is 0 to 2 and A is a 3 to 6 membered carbocyclic or heterocyclic ring, aromatic ring or heteroaromatic ring which may be optionally substituted with alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, and amino;

Y is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, cycloalkenyl, cycloalkenyloxy, alkenyloxyalkyl,

alkylaminoalkyl, and NR^9R^{10} wherein R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, nitro, amino, hydroxy, alkoxy, aryl, heterocyclyl, and aralkyl; R^9 and R^{10} can be taken together to form spacer groups independently selected from a linear moiety having a chain length of 2 to 7 atoms to form a C3 to C8 saturated heterocyclyl or a C4 to C8 partially saturated heterocyclyl substituted independently and optionally with one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups;

B is NR^5R^{11} wherein R^5 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, hydroxyl, sulfhydryl, OR^6, SR^6, alkyl, alkenyl, alkynyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, $CH_2SO_3^- M^+$, $CH_2CH_2SO_3^- M+$, $CH_2PO_3^{-2}\ 2M^+$, $CH_2CH_2PO_3^{-2}\ 2M^+$, $CH(OR^6)CF_3$, $S(O)R^{13}$, SO_2R^{13}, $P(O)(R^{30})_2$, $P(O)(R^{30})_3$, $C(O)R^{15}$, $C(S)R^{15}$, $CH_2OC(O)R^{15}$, $CH_2NR^{19}C(O)R^{15}$, $CH_2NR^{19}C(S)R^{15}$, $CH_2SC(O)R^{15}$, $CH_2SC(S)R^{15}$, $CH_2OC(O)GR^{15}$, $CH_2NR^{19}C(O)GR^{15}$, $CH_2NR^{19}C(S)GR^{15}$, $CH_2OC(S)GR^{15}$, $CH_2SC(S)GR^{15}$, OSO_2R^{13}, $OS(O)R^{13}$, $OC(S)R^{15}$, $SC(S)R^{15}$, $OC(S)GR^{15}$, $SC(S)GR^{15}$, $OC(O)R^{15}$, $SC(O)R^{15}$, $OC(O)GR^{15}$, $SC(O)GR^{15}$, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl,

aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboalkoxyalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, optionally substituted with one or more alkyl, haloalkyl, aryl, hydroxyl, thiol, amino, alkylamino, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, carboxy, aryloxy, heteroaryloxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups, provided that R^5 is selected from other than the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl and aryl unless J is S; when J is O one of R^1 and R^2 is other than hydrogen, lower alkyl, lower alkenyl or lower alkynyl or one of R^3 and R^4 are independently selected to be other than hydrogen, lower alkyl, lower alkenyl, lower alkynyl, OR^6 wherein R^6 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl, SO_2R^{13} wherein R^{13} is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl, $C(O)R^{15}$, wherein R^{15} is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl;

R^5 and R^1 can be taken together to form a spacer group selected from a linear moiety having a chain length of 1 to 4 atoms to form a C5 to C8 saturated heterocyclyl or a C5 to C8 partially saturated heterocyclyl optionally substituted with one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups;

R^5 and R^2 can be taken together to form spacer group selected from a linear moiety having a chain length of 1 to 4 atoms to form a C5 to C8 saturated

heterocyclyl or a C5 to C8 partially saturated heterocyclyl optionally substituted with one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups;

R^5 can be a spacer selected from a covalent bond or linear moiety having a chain length of 1 to 4 atoms to form a C5 to C10 saturated heterocyclyl or a C5 to C10 partially saturated heterocyclyl optionally substituted with one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups, and bonded to a hydroxyl, sulfhydryl, amino, carboxyl, or carbonyl substituent of group X,

R^{11} is selected from a heterocyclic ring in which at least one member of the ring is carbon and in which 1 to about 4 heteroatoms are independently selected from oxygen, nitrogen and sulfur and said heterocyclic ring may be optionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl,

dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, guanidino, amidino, and acylamino;

R^{19} and R^{20} are independently selected from the group consisting of hydrogen, hydroxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, acyl, aroyl, aralkanoyl, heteroaroyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, aralkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsufonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, dialkoxyphosphono, diaralkoxyphosphono, dialkoxyphosphonoalkyl, and diaralkoxyphosphonoalkyl provided that only one of R^{19} and R^{20} is hydrogen;

R^{19} and R^{20} can be taken together to form spacer groups independently selected from a linear moiety having a chain length of 2 to 7 atoms to form a C3 to C8 saturated cycloalkyl, a C3 to C8 partially saturated cycloalkyl, or a C3 to C8 heterocyclyl substituted independently and optionally with one or more alkyl,

haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups;

R^{30} is selected from the group consisting of hydroxy, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxyusulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and polyhydroxy compounds of carbon.

2. The compound as recited in Claim 1 and pharmaceutically acceptable salts and prodrugs, wherein:

J is O or S;

R^1 and R^2 are independently selected from the group consisting of hydrogen, hydroxyl, sulfhydryl, OR^6, SR^6, cyanoalkyl, dicyanoalkyl,

carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, $CH_2SO_3^- M^+$, $CH_2CH_2SO_3^- M+$, $CH_2PO_3^{-2}\ 2M^+$, $CH_2CH_2PO_3^{-2}\ 2M^+$, $CH(OR^6)CF_3$, $S(O)R^{13}$, SO_2R^{13}, $P(O)(R^{30})_2$, $P(O)(R^{30})_3$, $C(O)R^{15}$, $C(S)R^{15}$, $CH_2OC(O)R^{15}$, $CH_2SC(O)R^{15}$, $CH_2SC(S)R^{15}$, $CH_2OC(O)GR^{15}$, OSO_2R^{13}, $OS(O)R^{13}$, $OC(S)R^{15}$, $SC(S)R^{15}$, $OC(S)GR^{15}$, $SC(S)GR^{15}$, $OC(O)R^{15}$, $SC(O)R^{15}$ or $OC(O)GR^{15}$, all, except hydrogen, hydroxyl and sulfhydryl, optionally substituted by one or more alkyl, haloalkyl, aryl, hydroxyl, thiol, amino, alkylamino, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, carboxy, aryloxy, heteroaryloxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups; provided that only one of R^1 and R^2 can be hydrogen, alkyl, alkenyl and alkynyl unless J is S; when J is O, R^3 and R^4 are independently selected to be other than hydrogen, lower alkyl, lower alkenyl, lower alkynyl, OR^6 wherein R^6 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl, SO_2R^{13} wherein R^{13} is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, and $C(O)R^{15}$, wherein R^{15} is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl, or B is NR^5R^{11} wherein R^5 is selected from other than the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl and aryl;

R^1 and R^2 can be taken together to form imines containing the substituent of formula $R^{19}(R^{20})C=$;

R^3 and R^4 are independently selected from the group consisting of hydrogen, hydroxyl, sulfhydryl, OR^6, SR^6, $CH_2SO_3^- M^+$, $CH_2CH_2SO_3^- M+$,

$CH_2PO_3^{-2}\ 2M^+$, $CH_2CH_2PO_3^{-2}\ 2M^+$, $S(O)R^{13}$, SO_2R^{13}, $P(O)(R^{30})_2$, $P(O)(R^{30})_3$, $C(O)R^{15}$, $C(S)R^{15}$, $CH_2OC(O)R^{15}$, OSO_2R^{13}, $OS(O)R^{13}$, $OC(S)R^{15}$, $SC(S)R^{15}$, $OC(S)GR^{15}$, $SC(S)GR^{15}$, $OC(O)R^{15}$, $SC(O)R^{15}$, $OC(O)GR^{15}$, and $SC(O)GR^{15}$; provided that when J is O, R^6 cannot be lower alkyl, lower alkenyl, lower alkynyl or aryl and R^3 or R^4 cannot be OR^6, R^{13} cannot be lower alkyl, lower alkenyl, lower alkynyl or aryl when R^3 or R^4 is SO_2R^{13}; R^{15} cannot be lower alkyl, lower alkenyl, lower alkynyl or aryl when R^3 or R^4 is COR^{15}; provided only one of R^3 and R^4 can be hydrogen, lower alkyl, lower alkenyl, or lower alkynyl unless R^1 and R^2 are independently selected from other than hydrogen, or B is NR^5R^{11} wherein R^5 is selected from other than the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl and aryl;

G is selected from the group consisting of O, S, CH_2, CHR^{15}, $C(R^{15})_2$, NH, and NR^{15};

R^6 is selected from the group consisting of hydroxyalkyl, heteroaryloxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl,

diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxyusulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and alkylpolyhydroxy;

R^{13} is selected from the group consisting of aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxyusulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural or synthetic amino acids, and alkylpolyhydroxy;

R^{15} is selected from the group consisting of hydrido, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl,

haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxyusulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and alkylpolyhydroxy;

M^+ is a pharmaceutically acceptable cations;

X is selected from the group consisting of alkylene, alkenylene, and alkynylene groups which may be optionally substituted with one or more alkyl, alkoxy, hydroxy, sulfhydryl, halogen, trifluoromethyl, nitro, cyano, and amino; or

X is selected from the group consisting of $-(CH_2)_pQ(CH_2)_r-$ wherein p is 1 to 3, r is 1 to 3 and Q is oxygen, C=O, $S(O)_t$ wherein t is 0 to 2, $P(O)R^{21}$ wherein R^{21} is hydroxyl or alkyl which may be optionally substituted with one or more alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, amino, carboxy, or $N(R^{12})_n$ wherein n is 1 to 2 and R^{12} is hydrogen, oxy, hydroxyl or alkyl which may be optionally substituted with one or more alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, amino; or

X is selected from the group consisting of $-(CH_2)_sA(CH_2)_v-$ wherein s is O to 2, v is 0 to 2 and A is a 3 to 6 membered carbocyclic or heterocyclic ring,

aromatic ring or heteroaromatic ring which may be optionally substituted with alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, and amino;

Y is selected from the group consisting of alkyl, haloalkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, cycloalkenyl, cycloalkenyloxy, alkenyloxyalkyl, and alkylaminoalkyl;

Y can be NR^9R^{10} wherein R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, nitro, amino, hydroxy, alkoxy, aryl, heterocyclyl, and aralkyl; R^9 and R^{10} can be taken together to form spacer groups independently selected from a linear moiety having a chain length of 2 to 7 atoms to form a C3 to C8 saturated heterocyclyl or a C4 to C8 partially saturated heterocyclyl substituted independently and optionally with one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups;

B is NR^5R^{11} wherein R^5 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, hydroxyl, sulfhydryl, OR^6, SR^6, alkyl, alkenyl, alkynyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, $CH_2SO_3^- M^+$, $CH_2CH_2SO_3^- M+$, $CH_2PO_3^{-2}\ 2M^+$, $CH_2CH_2PO_3^{-2}\ 2M^+$, $CH(OR^6)CF_3$, $S(O)R^{13}$, SO_2R^{13}, $P(O)(R^{30})_2$, $P(O)(R^{30})_3$, $C(O)R^{15}$, $C(S)R^{15}$, $CH_2OC(O)R^{15}$, $CH_2NR^{19}C(O)R^{15}$, $CH_2NR^{19}C(S)R^{15}$, $CH_2SC(O)R^{15}$, $CH_2SC(S)R^{15}$, $CH_2OC(O)GR^{15}$, $CH_2NR^{19}C(O)GR^{15}$, $CH_2NR^{19}C(S)GR^{15}$, $CH_2OC(S)GR^{15}$, $CH_2SC(S)GR^{15}$, OSO_2R^{13}, $OS(O)R^{13}$, $OC(S)R^{15}$, $SC(S)R^{15}$, $OC(S)GR^{15}$, $SC(S)GR^{15}$,

$OC(O)R^{15}$, $SC(O)R^{15}$, $OC(O)GR^{15}$, $SC(O)GR^{15}$, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboalkoxyalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, optionally substituted with one or more alkyl, haloalkyl, aryl, hydroxyl, thiol, amino, alkylamino, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, carboxy, aryloxy, heteroaryloxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups, provided that R^5 is selected from other than the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl and aryl unless J is S; when J is O one of R^1 and R^2 is other than hydrogen, lower alkyl, lower alkenyl or lower alkynyl or one of R^3 and R^4 are independently selected to be other than hydrogen, lower alkyl, lower alkenyl, lower alkynyl, OR^6 wherein R^6 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl, SO_2R^{13} wherein R^{13} is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl, $C(O)R^{15}$, wherein R^{15} is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl;

R^5 and R^1 can be taken together to form a spacer group selected from a linear moiety having a chain length of 1 to 4 atoms to form a C5 to C8 saturated

heterocyclyl or a C5 to C8 partially saturated heterocyclyl optionally substituted with one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups;

R^5 and R^2 can be taken together to form spacer group selected from a linear moiety having a chain length of 1 to 4 atoms to form a C5 to C8 saturated heterocyclyl or a C5 to C8 partially saturated heterocyclyl optionally substituted with one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups;

R^5 can be a spacer selected from a covalent bond or linear moiety having a chain length of 1 to 4 atoms to form a C5 to C10 saturated heterocyclyl or a C5 to C10 partially saturated heterocyclyl optionally substituted with one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups, and bonded to a hydroxyl, sulfhydryl, amino, carboxyl, or carbonyl substituent of group X,

R^{11} is selected from a heterocyclic ring in which at least one member of the ring is carbon and in which 1 to about 4 heteroatoms are independently selected from oxygen, nitrogen and sulfur and said heterocyclic ring may be optionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl,

hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, guanidino, amidino, and acylamino;

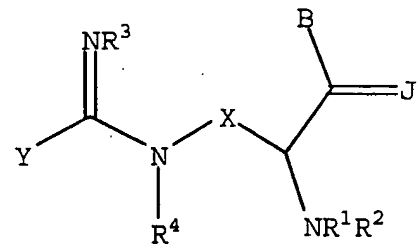
R^{19} and R^{20} are independently selected from the group consisting of hydrogen, hydroxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, acyl, aroyl, aralkanoyl, heteroaroyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, aralkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsufonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, dialkoxyphosphono, diaralkoxyphosphono,

dialkoxyphosphonoalkyl, and diaralkoxyphosphonoalkyl provided that only one of R^{19} and R^{20} is hydrogen;

R^{19} and R^{20} can be taken together to form spacer groups independently selected from a linear moiety having a chain length of 2 to 7 atoms to form a C3 to C8 saturated cycloalkyl, a C3 to C8 partially saturated cycloalkyl, or a C3 to C8 heterocyclyl substituted independently and optionally with one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups;

R^{30} is selected from hydroxy, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and polyhydroxy compounds of carbon.

3. A compound having the formula



and pharmaceutically acceptable salts and prodrugs,

wherein:

J is O ;

R^1 and R^2 are independently selected from the group consisting of hydrogen, hydroxyl, sulfhydryl, OR^6, SR^6, $CH_2SC(O)R^{15}$, $CH_2SC(S)R^{15}$, $CH_2OC(O)GR^{15}$, OSO_2R^{13}, $OS(O)R^{13}$, $OC(S)R^{15}$, $SC(S)R^{15}$, $OC(S)GR^{15}$, $SC(S)GR^{15}$, $OC(O)R^{15}$, $SC(O)R^{15}$ and $OC(O)GR^{15}$, all, except hydrogen, hydroxyl and sulfhydryl, may be optionally substituted by one or more alkyl, haloalkyl, aryl, hydroxyl, thiol, amino, alkylamino, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, carboxy, aryloxy, heteroaryloxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups; provided that only one of R^1 and R^2 can be hydrogen, alkyl, alkenyl and alkynyl;

R^1 and R^2 can be taken together to form imines containing the substituent of formula $R^{19}(R^{20})C=$;

R^3 and R^4 are independently selected from the group consisting of hydroxyl, sulfhydryl, SR^6, $S(O)R^{13}$, OSO_2R^{13}, $OS(O)R^{13}$, $OC(S)R^{15}$, $SC(S)R^{15}$, $OC(S)GR^{15}$, $SC(S)GR^{15}$, $OC(O)R^{15}$, $SC(O)R^{15}$, $OC(O)GR^{15}$, and $SC(O)GR^{15}$;

provided R^6 cannot be lower alkyl, lower alkenyl, lower alkynyl or aryl, R^3 or R^4 cannot be OR^6, R^{13} cannot be lower alkyl, lower alkenyl, lower alkynyl or aryl when R^3 or R^4 is SO_2R^{13}, R^{15} cannot be lower alkyl, lower alkenyl, lower alkynyl or aryl when R^3 or R^4 is COR^{15}; provided only one of R^3 and R^4 can be hydrogen, lower alkyl, lower alkenyl, or lower alkynyl unless R^1 and R^2 are independently selected from other than hydrogen, or B is NR^5R^{11} wherein R^5 is selected from other than the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl and aryl;

G is selected from the group consisting of O, S, CH_2, CHR^{15}, $C(R^{15})_2$, NH, and NR^{15};

R^6 is selected from the group consisting of hydroxyalkyl, heteroaryloxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and alkylpolyhydroxy;

R^{13} is selected from the group consisting of aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxyusulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and alkylpolyhydroxy;

R^{15} is independently selected from the group consisting of hydrido, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl,

formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and alkylpolyhydroxy;

M^+ is a pharmaceutically acceptable cations;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, and $-(CH_2)_pQ(CH_2)_r-$ wherein p is 1 to 3, r is 1 to 3 and Q is selected from the group consisting of oxygen, C=O, and $S(O)_t$ wherein t is 0 to 2, wherein each may be optionally substituted with one or more alkyl, alkoxy, hydroxy, sulfhydryl, halogen, trifluoromethyl, nitro, cyano, amino, $P(O)R^{21}$ wherein R^{21} is hydroxyl or alkyl which may be optionally substituted with one or more alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, amino, carboxy, or $N(R^{12})_n$ wherein n is 1 to 2 and R^{12} is hydrogen, oxy, hydroxyl or alkyl which may be optionally substituted with one or more alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, and amino;

B is NR^5R^{11} wherein R^5 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, hydroxyl, sulfhydryl, OR^6, SR^6, alkyl, alkenyl, alkynyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, $CH_2SO_3^- M^+$, $CH_2CH_2SO_3^- M+$,

$CH_2PO_3^{-2}\,2M^+$, $CH_2CH_2PO_3^{-2}\,2M^+$, $CH(OR^6)CF_3$, $S(O)R^{13}$, SO_2R^{13}, $C(O)R^{15}$, $C(S)R^{15}$, $CH_2OC(O)R^{15}$, $CH_2NR^{19}C(O)R^{15}$, $CH_2NR^{19}C(S)R^{15}$, $CH_2SC(O)R^{15}$, $CH_2SC(S)R^{15}$, $CH_2OC(O)GR^{15}$, $CH_2NR^{19}C(O)GR^{15}$, $CH_2NR^{19}C(S)GR^{15}$, $CH_2OC(S)GR^{15}$, $CH_2SC(S)GR^{15}$, OSO_2R^{13}, $OS(O)R^{13}$, $OC(S)R^{15}$, $SC(S)R^{15}$, $OC(S)GR^{15}$, $SC(S)GR^{15}$, $OC(O)R^{15}$, $SC(O)R^{15}$, $OC(O)GR^{15}$, $SC(O)GR^{15}$, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboalkoxyalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxyusulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, optionally substituted with one or more alkyl, haloalkyl, aryl, hydroxyl, thiol, amino, alkylamino, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, carboxy, aryloxy, heteroaryloxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups, provided that R^5 is selected from other than the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl and aryl when one of R^1 and R^2 is other than hydrogen, lower alkyl, lower alkenyl or lower alkynyl or one of R^3 and R^4 are independently selected to be other than hydrogen, lower alkyl, lower alkenyl, lower alkynyl, OR^6 wherein R^6 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, or SO_2R^{13} wherein R^{13}

is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl, $C(O)R^{15}$, wherein R^{15} is hydrogen, lower alkyl, lower alkenyl, lower alkynyl or aryl;

R^5 can be a spacer selected from a covalent bond or linear moiety having a chain length of 1 to 4 atoms to form a C5 to C10 saturated heterocyclyl or a C5 to C10 partially saturated heterocyclyl optionally substituted with one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups,

R^{11} is selected from a heterocyclic ring in which at least one member of the ring is carbon and in which 1 to about 4 heteroatoms are independently selected from oxygen, nitrogen and sulfur and said heterocyclic ring may be optionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl,

diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, guanidino, amidino, and acylamino;

R^{19} and R^{20} are independently selected from the group consisting of hydrogen, hydroxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, acyl, aroyl, aralkanoyl, heteroaroyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, aralkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsufonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, dialkoxyphosphono, diaralkoxyphosphono, dialkoxyphosphonoalkyl, and diaralkoxyphosphonoalkyl provided that only one of R^{19} and R^{20} is hydrogen;

R^{19} and R^{20} can be taken together to form spacer groups independently selected from a linear moiety having a chain length of 2 to 7 atoms to form a C3 to C8 saturated carbocyclyl, a C3 to C8 partially saturated carbocyclyl, a C3 to C8 saturated heterocyclyl or a C4 to C8 partially saturated heterocyclyl substituted independently and optionally with, for example, one or more alkyl, haloalkyl, aryl,

heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups.

4. The compound as recited in Claim 3 and pharmaceutically acceptable salts and prodrugs, wherein:

J is O ;

R^1 and R^2 are independently selected from the group consisting of hydrogen, hydroxyl, sulfhydryl, OR^6, SR^6, OSO_2R^{13}, $OS(O)R^{13}$, $OC(S)R^{15}$, $SC(S)R^{15}$, $OC(O)R^{15}$, and $SC(O)R^{15}$ all, except hydrogen, hydroxyl and sulfhydryl, may be optionally substituted by one or more alkyl, haloalkyl, aryl, hydroxyl, thiol, amino, alkylamino, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, carboxy, aryloxy, heteroaryloxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups; provided that only one of R^1 and R^2 can be hydrogen, alkyl, alkenyl and alkynyl;

R^3 and R^4 are independently selected from the group consisting of hydroxyl, sulfhydryl, SR^6, $S(O)R^{13}$, OSO_2R^{13}, $OS(O)R^{13}$, $OC(S)R^{15}$, $SC(S)R^{15}$, $OC(O)R^{15}$, and $SC(O)R^{15}$; provided R^6 cannot be lower alkyl, lower alkenyl, lower alkynyl or aryl, R^3 or R^4 cannot be OR^6, R^{13} cannot be lower alkyl, lower alkenyl, or lower alkynyl;

R^6 is selected from the group consisting of hydroxyalkyl, heteroaryloxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl,

cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and alkylpolyhydroxy;

R^{13} is selected from the group consisting of aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxyusulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and alkylpolyhydroxy;

R^{15} is selected from the group consisting of hydrido, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and alkylpolyhydroxy;

M^+ is a pharmaceutically acceptable cations;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, and $-(CH_2)_pQ(CH_2)_r-$ wherein p is 1 to 3, r is 1 to 3 and Q is selected from the group consisting of oxygen, C=O, and $S(O)_t$ wherein t is 0 to 2, wherein each may be optionally substituted with one or more alkyl, alkoxy, hydroxy, sulfhydryl, halogen, trifluoromethyl, nitro, cyano, and amino;

B is NR^5R^{11} wherein R^5 is selected from the group consisting of hydroxyl, sulfhydryl, OR^6, SR^6, alkyl, alkenyl, alkynyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, $CH_2SO_3^- M^+$, $CH_2CH_2SO_3^- M+$, $CH_2PO_3^{-2} 2M^+$, $CH_2CH_2PO_3^{-2} 2M^+$, $CH(OR^6)CF_3$, $S(O)R^{13}$, SO_2R^{13}, $C(O)R^{15}$, $C(S)R^{15}$, $CH_2OC(O)R^{15}$, $CH_2SC(O)R^{15}$, $CH_2SC(S)R^{15}$, $CH_2OC(O)GR^{15}$, $CH_2OC(S)GR^{15}$, $CH_2SC(S)GR^{15}$, OSO_2R^{13}, $OS(O)R^{13}$, $OC(S)R^{15}$, $SC(S)R^{15}$, $OC(S)GR^{15}$, $OC(O)R^{15}$, $SC(O)R^{15}$, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboalkoxyalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxyusulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, optionally substituted with one or more alkyl, haloalkyl, aryl, hydroxyl, thiol, amino, alkylamino, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, carboxy, aryloxy, heteroaryloxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups;

R^{11} is selected from the group consisting of from a heterocyclic ring in which at least one member of the ring is carbon and in which 1 to about 4 heteroatoms are independently selected from oxygen, nitrogen and sulfur and said heterocyclic ring may be optionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, guanidino, amidino, and acylamino.

5. The compound as recited in Claim 3 and pharmaceutically acceptable salts and prodrugs, wherein:

J is O;

R^1 and R^2 are independently selected from the group consisting of hydrogen, hydroxyl, sulfhydryl, OR^6, SR^6, all, except hydrogen, hydroxyl and sulfhydryl, may be optionally substituted by one or more alkyl, haloalkyl, aryl, hydroxyl, thiol, amino, alkylamino, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, carboxy, aryloxy, heteroaryloxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups; provided that only one of R^1 and R^2 can be hydrogen, alkyl, alkenyl and alkynyl;

R^3 and R^4 are independently selected from the group consisting of hydroxyl, sulfhydryl, and SR^6;

R^6 is independently selected from the group consisting of hydroxyalkyl, heteroaryloxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and alkylpolyhydroxy;

M^+ is a pharmaceutically acceptable cations;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, and $-(CH_2)_pQ(CH_2)_r-$ wherein p is 1 to 3, r is 1 to 3 and Q is selected from the group consisting of oxygen, C=O, and $S(O)_t$ wherein t is 0 to 2, wherein each may be optionally substituted with one or more alkyl, alkoxy, hydroxy, sulfhydryl, halogen, trifluoromethyl, nitro, cyano, and amino;

B is NR^5R^{11} wherein R^5 is selected from the group consisting of hydroxyl, sulfhydryl, OR^6, SR^6, alkyl, alkenyl, alkynyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, $CH_2SO_3^- M^+$, $CH_2CH_2SO_3^- M+$, $CH_2PO_3^{-2}\ 2M^+$, $CH_2CH_2PO_3^{-2}\ 2M^+$, $CH(OR^6)CF_3$, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboalkoxyalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxyusulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, optionally substituted with one or more alkyl, haloalkyl, aryl, hydroxyl, thiol, amino, alkylamino, heteroaryl,

alkoxyalkyl, alkoxy, haloalkoxy, carboxy, aryloxy, heteroaryloxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups;

R^{11} is selected from a heterocyclic ring in which at least one member of the ring is carbon and in which 1 to about 4 heteroatoms are independently selected from oxygen, nitrogen and sulfur and said heterocyclic ring may be optionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, guanidino, amidino, and acylamino.

6. The compound as recited in Claim 3 and pharmaceutically acceptable salts and prodrugs, wherein:

J is O;

R^1 and R^2 are independently selected from the group consisting of hydrogen, hydroxyl, sulfhydryl, OR^6, SR^6, all, except hydrogen, hydroxyl and sulfhydryl, may be optionally substituted by one or more alkyl, haloalkyl, aryl, hydroxyl, thiol, amino, alkylamino, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, carboxy, aryloxy, heteroaryloxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups; provided that only one of R^1 and R^2 can be hydrogen, alkyl, alkenyl and alkynyl;

R^3 and R^4 are independently selected from the group consisting of hydroxyl, sulfhydryl, and SR^6;

R^6 is selected from the group consisting of hydroxyalkyl, heteroaryloxyalkyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl,

sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino, and sulfonylalkylamino.

7. A compound as recited in Claim 3 wherein said compound is selected from the group consisting of:

L-N-(2-cyanoethyl)-N-(2-thiazolyl)- e-N (methoxyiminoethyl)lysinamide dihydrochloride;

L-N-(2-dimethylamino)-N-(2-pyridyl)- e-N-(iminoethyl)lysinamide tetrahydrochloride;

N-(2-acetoxyethyl)-N-(2-thiazolyl)-S-(2-(N-(2-acetoxyiminoethyl)amino)ethyl)-L-Cysteinamide;

N-acetyl-N-(4-pyridyl)-S-(2-(N-(iminoethyl)amino)ethyl)-L-Cysteinamide;

N-(phenyl)-N-(2-imidazolyl)-a-N-(2,2-dicyanoethyl)-e-(N-Boc-1-iminoethyl)-L-Lysinamide;

N-(phenyl)-N-(2-imidazolyl)-a-N-(2,2-dicyanoethyl)-e-(1-iminoethyl)-L-lysinamide trihydrochloride;

N-hydroxy-N-(5-tetrazoyl)-e-(N-(1-iminoethyl))amino- a-(N-hydroxy-N-acetamido)hexanamide;

N-(2-thiazolyl)-e-(N-(1-oximinoethyl)amino)-a-(N-hydroxy-N-acetamido)hexanamide;

N-(2-imidazolyl)- S-(2-(N-(2-fluoro-1-oximinoethyl)amino)ethyl)- a-N-(4-morpholinomethylbenzoyl)-D,L-homocysteinamide;

N-(3-quiniclidinyl)- d-N-(1-imino-1-cyclopropylmethyl)-a-(N-methoxyformyl)-D,L-methylornithinamide;

N-(2-g-butyrolactone)-a-(N-methansulfonyl)-*ortho*-(N-(1-oximinoethyl))aminomethyl)phenylalaninamide;

N-(2-pyrimidinyl)- 3-(5-(N-(1-iminoethyl)amino)methyl)thiophenyl)-2-acetamidopropionamide;

N-methyl-N-(2-pyridyl)-α-(N-cyclopentyl)-α-N-(3,3,3-trifluoropropanoyl)-O-(2-(N-(1-iminoethyl)amino)ethyl)-L-serinamide;

N-methyl-N-(4-imidazolyl)-α-(N-(1-pyrrolylethylenyl))-O-(2-(N-(1-(O-(methoxycarbonyl) oximino)ethyl)amino)ethyl)-α-(N-ethanesulfonyl)-L-serinamide;

sodium α-N-(N-methyl-N-(4-thiazolyl)-O-(2-(N-(2-fluoro-1-iminoethyl)amino)ethyl)-L-serinamido)methanesulfonate;

3-N-(5-tetrazolyl)-5-(3-(N-(1-(O-propionyloximino)ethyl)amino)prop-1-ynyl)hydantoin trifluoroacetate;

1-N-(2-imidazolyl)-3-(2-(N-(1-iminoethyl)amino)ethoxy)methyl)-6-(2-methiothioethyl)-2-oxo-3,6-dihydropyrazine trihydrochloride;

N-methyl-N-(5-tetrazolyl)-S-(2-(N-phosphonomethyl-N-(1-iminoethyl)amino)ethyl)-L-cysteinamide;

N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-a-((N-ethoxycarbonyl)amino)thionohexanamide;

N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-(N-(2,2,2-trifluoro-1-ethoxyethyl))aminohexanamide;

N-methyl-N-(5-tetrazolyl)-S-(2-(1-(N-(benzoyloxymethyl)imino)ethyl)-N-hydroxy)aminoethyl)-L-cysteinamide;

N-methyl-N-(5-tetrazolyl)- a-N-benzoyl- e-N-(2-(1-(N-(benzoyloxymethyl)imino)ethyl))- e-N-(1-propyl)-L-Lysine;

N-methyl-N-(5-(tetrazolyl)-ε-N-(2-fluoro-1-iminoethyl)-ε-N-(N,N'N'-trimethylureido-N-methylene)-L-Lysinamide;

N-methyl-N-(5-tetrazolyl)-ε-N-(2-fluoro-1-iminoethyl)-α-N-(N,N'N'-trimethylureido-N-methylene)-L-Lysinamide;

N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-(N-(phenylalaninyl)amino)hexanamide; and

N-acetoxymethyl-N-(5-tetrazolyl)-ε-N-(iminoethyl)-L-Lysinamide.

8. A pharmaceutical composition comprising a compound of one of claims 1,2,3,4,5,6 and 7 together with one or more pharmaceutically acceptable carriers.

9. A method of inhibiting nitric oxide synthesis in a subject in need of such inhibition by administering a therapeutically effective amount of a compound of one of claims 1,2,3,4,5,6, and 7.

10. A method of selectively inhibiting nitric oxide synthesis produced by inducible NO synthase over nitric oxide produced by the constitutive forms of NO synthase in a subject in need of such selective inhibition by administering a therapeutically effective amount of a compound of one of claims 1,2,3,4,5,6 and 7.

11. A method of lowering nitric oxide levels in a subject in need of such by administering a therapeutically effective amount of a compound of one of claims 1,2,3,4,5,6 and 7.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D257/06 C07D277/46 C07D213/75 C07D233/88 C07D453/02
C07D307/32 C07D249/04 C07F9/6524 C07D409/12 C07D403/12
C07D407/12 C07D403/04 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07F C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 15120 A (SEARLE & CO ;HALLINAN E ANN (US); HANSEN DONALD W JR (US); TSYMBAL) 23 May 1996 (1996-05-23) cited in the application claims ---	1-11
Y	WO 95 24382 A (SEARLE & CO ;HALLINAN E ANN (US); TJOENG FOE S (US); FOK KAM F (US) 14 September 1995 (1995-09-14) cited in the application claims ---	1-11
A	WO 95 25717 A (SEARLE & CO ;CURRIE MARK G (US); WEBBER KEITH (US); TJOENG FOE S () 28 September 1995 (1995-09-28) cited in the application claims -----	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 February 2000	01/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/21468

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9-11
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 9-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter [national] Application No
PCT/US 99/21468

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9615120	A	23-05-1996	US	5684008	A	04-11-1997
			AU	696527	B	10-09-1998
			AU	3971195	A	06-06-1996
			BR	9509629	A	06-01-1998
			CA	2203237	A	23-05-1996
			CN	1171104	A	21-01-1998
			EP	0790987	A	27-08-1997
			JP	10508847	T	02-09-1998
			NZ	296019	A	24-09-1998
			US	5919787	A	06-07-1999
			US	5854251	A	29-12-1998
WO 9524382	A	14-09-1995	AU	2115695	A	25-09-1995
			CA	2184691	A	14-09-1995
			EP	0749418	A	27-12-1996
WO 9525717	A	28-09-1995	AU	2190895	A	09-10-1995
			CA	2186224	A	28-09-1995
			DE	69514341	D	10-02-2000
			EP	0751930	A	08-01-1997